

PROTOCOL No. PM-8450
COVANCE STUDY No. 12226-8450
UPDATED FINAL DRAFT
RESEARCH STUDY REPORT
22 OCTOBER 2003

VOL 2 OF 14

PM3006438172

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

14. TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN TEXT

14.1 Statistical Analyses

14.1.1 Intra- and Inter-Subject Variability

Table 14.1.1-1
Covariance Structure Selection Using Akaike's Information Criterion for Full Model
(Page 1 of 6)

Biomarker	Unit	Covariance Structure	Akaike's Information Criterion (smaller is better)
Acetonitrile in blood	(µg/mL)/2	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	163.6
		COMPOUND SYMMETRY BY GROUP	187.4
		HETEROGENEOUS COMPOUND SYMMETRY	234.2
		COMPOUND SYMMETRY	248.2
Carboxyhemoglobin	% saturation	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	682.4
		COMPOUND SYMMETRY BY GROUP	833.6
		COMPOUND SYMMETRY	1388.6
		HETEROGENEOUS COMPOUND SYMMETRY	1391.9
3-Aminobiphenyl-Hb adduct	pg/g hemoglobin	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	724.6
		COMPOUND SYMMETRY BY GROUP	781.7
		HETEROGENEOUS COMPOUND SYMMETRY	1204.6
		COMPOUND SYMMETRY	1309.1
4-Aminobiphenyl-Hb adduct	pg/g hemoglobin	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	1657.1
		COMPOUND SYMMETRY BY GROUP	1770.8
		HETEROGENEOUS COMPOUND SYMMETRY	2160.5

NOTE: In the case of convergence problems, different units were used and/or the same covariance structure was assumed for smokers and nonsmokers (i.e., the 'by group' structure was not used).

Table 14.1.1-1
Covariance Structure Selection Using Akaike's Information Criterion for Full Model
(Page 2 of 6)

Biomarker	Unit	Covariance Structure	Akaike's Information Criterion (smaller is better)
4-Aminobiphenyl-Hb adduct	pg/g hemoglobin	COMPOUND SYMMETRY	2398.4
Sum of Nicotine and Nicotine metabolites	(nmol/mg Creatinine)/10	COMPOUND SYMMETRY BY GROUP	-260.9
		COMPOUND SYMMETRY	1261.2
		HETEROGENEOUS COMPOUND SYMMETRY	1262.0
Nicotine	nmol/mg Creatinine	COMPOUND SYMMETRY BY GROUP	740.8
		HETEROGENEOUS COMPOUND SYMMETRY	1975.8
		COMPOUND SYMMETRY	1990.8
Cotinine	nmol/mg Creatinine	COMPOUND SYMMETRY BY GROUP	-31.2
		HETEROGENEOUS COMPOUND SYMMETRY	1694.3
		COMPOUND SYMMETRY	1694.7
Trans-3-hydroxycotinine	nmol/mg Creatinine	COMPOUND SYMMETRY	2242.7
		HETEROGENEOUS COMPOUND SYMMETRY	2245.0
Trans-3-hydroxycotinine-O-glucuronide	nmol/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY	1665.9
		COMPOUND SYMMETRY	1694.2
NNAL plus NNAL-gluc	pmol/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	54.6

NOTE: In the case of convergence problems, different units were used and/or the same covariance structure was assumed for smokers and nonsmokers (i.e., the 'by group' structure was not used).

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

Table 14.1.1-1
 Covariance Structure Selection Using Akaike's Information Criterion for Full Model
 (Page 3 of 6)

Biomarker	Unit	Covariance Structure	Akaike's Information Criterion (smaller is better)
NNAL plus NNAL-gluc	pmol/mg Creatinine	COMPOUND SYMMETRY BY GROUP	78.4
		HETEROGENEOUS COMPOUND SYMMETRY	788.8
		COMPOUND SYMMETRY	792.2
NNAL	pmol/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	-397.1
		COMPOUND SYMMETRY BY GROUP	-390.8
		HETEROGENEOUS COMPOUND SYMMETRY	222.5
		COMPOUND SYMMETRY	229.1
NNAL-O-glucuronide	pmol/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	-12.5
		COMPOUND SYMMETRY BY GROUP	38.4
		COMPOUND SYMMETRY	681.5
		HETEROGENEOUS COMPOUND SYMMETRY	683.1
Nicotine-N-glucuronide	nmol/mg Creatinine	COMPOUND SYMMETRY BY GROUP	-318.3
		HETEROGENEOUS COMPOUND SYMMETRY	1150.9
		COMPOUND SYMMETRY	1166.0
Cotinine-N-glucuronide	nmol/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY	1874.9

NOTE: In the case of convergence problems, different units were used and/or the same covariance structure was assumed for smokers and nonsmokers (i.e., the 'by group' structure was not used).

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

Table 14.1.1-1
Covariance Structure Selection Using Akaike's Information Criterion for Full Model
(Page 4 of 6)

Biomarker	Unit	Covariance Structure	Akaike's Information Criterion (smaller is better)
Cotinine-N-glucuronide	nmol/mg Creatinine	COMPOUND SYMMETRY	1876.8
Acetonitrile in exhalate	nL/L @20 °C and 1 atm	COMPOUND SYMMETRY	7384.3
Carbon monoxide	ppm	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	2355.1
		COMPOUND SYMMETRY BY GROUP	2367.4
		COMPOUND SYMMETRY	2875.8
		HETEROGENEOUS COMPOUND SYMMETRY	2878.4
HDL-cholesterol	mg/dL	HETEROGENEOUS COMPOUND SYMMETRY	2311.0
		COMPOUND SYMMETRY	2313.9
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	2315.3
		COMPOUND SYMMETRY BY GROUP	2317.4
LDL-cholesterol	mg/dL	COMPOUND SYMMETRY	3014.1
		HETEROGENEOUS COMPOUND SYMMETRY	3014.8
		COMPOUND SYMMETRY BY GROUP	3017.6
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	3017.9
Fibrinogen	mg/dL	HETEROGENEOUS COMPOUND SYMMETRY	3757.7
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	3757.8

NOTE: In the case of convergence problems, different units were used and/or the same covariance structure was assumed for smokers and nonsmokers (i.e., the 'by group' structure was not used).

Table 14.1.1-1
Covariance Structure Selection Using Akaike's Information Criterion for Full Model
(Page 5 of 6)

Biomarker	Unit	Covariance Structure	Akaike's Information Criterion (smaller is better)
Fibrinogen	mg/dL	COMPOUND SYMMETRY BY GROUP	3762.7
		COMPOUND SYMMETRY	3765.8
C-reactive protein	mg/dL	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	461.7
		HETEROGENEOUS COMPOUND SYMMETRY	493.6
		COMPOUND SYMMETRY BY GROUP	499.1
		COMPOUND SYMMETRY	520.2
Malondialdehyde in blood	μmol/L	HETEROGENEOUS COMPOUND SYMMETRY	-667.3
		COMPOUND SYMMETRY	-665.6
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	-664.3
		COMPOUND SYMMETRY BY GROUP	-661.6
11-Dehydro-thromboxane B2	ng/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	154.2
		COMPOUND SYMMETRY BY GROUP	156.4
		HETEROGENEOUS COMPOUND SYMMETRY	218.4
		COMPOUND SYMMETRY	218.8
8-Epi-prostaglandin F2α	ng/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	470.3
		COMPOUND SYMMETRY BY GROUP	472.8

NOTE: In the case of convergence problems, different units were used and/or the same covariance structure was assumed for smokers and nonsmokers (i.e., the 'by group' structure was not used).

Table 14.1.1-1
 Covariance Structure Selection Using Akaike's Information Criterion for Full Model
 (Page 6 of 6)

Biomarker	Unit	Covariance Structure	Akaike's Information Criterion (smaller is better)
8-Epi-prostaglandin F2 α	ng/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY	606.9
		COMPOUND SYMMETRY	620.7
Malondialdehyde in urine	nmol/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	886.6
		HETEROGENEOUS COMPOUND SYMMETRY	887.4
		COMPOUND SYMMETRY	915.4
		COMPOUND SYMMETRY BY GROUP	918.5

NOTE: In the case of convergence problems, different units were used and/or the same covariance structure was assumed for smokers and nonsmokers (i.e., the 'by group' structure was not used).

Table 14.1.1-2
Covariance Parameter Estimates for Full Model
(Page 1 of 7)

Biomarker	Unit	Covariance Structure	Group	Covariance Parameter	Estimate	P-Value *
Acetonitrile in blood	(µg/mL)/2	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(1)	0.08704	0.0029
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(2)	0.1075	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(3)	0.2778	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(4)	0.1739	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	CSH	0.1739	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(1)	0.07987	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(2)	0.03062	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(3)	0.04670	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(4)	0.05347	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	CSH	0.1199	
Carboxyhemoglobin	% saturation	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(1)	9.4064	<0.0001
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(2)	8.9892	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(3)	9.2187	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(4)	8.4373	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	CSH	0.8697	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(1)	0.02013	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(2)	0.02341	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(3)	0.2423	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(4)	0.04160	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	CSH	0.3136	
3-Aminobiphenyl-Hb adduct	pg/g hemoglobin	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(1)	10.4490	0.3553

* P-value to test if the off diagonal terms of the fitted covariance structure are zero based on likelihood ratio test.

Table 14.1.1-2
Covariance Parameter Estimates for Full Model
(Page 2 of 7)

Biomarker	Unit	Covariance Structure	Group	Covariance Parameter	Estimate	P-Value ^a
3-Aminobiphenyl-Hb adduct	pg/g hemoglobin	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(2)	95.0955	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	CSH	0.2078	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(1)	0.2509	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(2)	0.1109	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	CSH	-0.02312	
4-Aminobiphenyl-Hb adduct	pg/g hemoglobin	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(1)	390.87	<0.0001
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(2)	14609	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	CSH	-0.00442	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(1)	12.7164	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(2)	20.4580	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	CSH	0.7381	
Sum of Nicotine and Nicotine metabolites	(nmol/mg Creatinine)/10	COMPOUND SYMMETRY BY GROUP	Smokers	Variance	1.5660	<0.0001
		COMPOUND SYMMETRY BY GROUP	Smokers	CS	17.5734	
		COMPOUND SYMMETRY BY GROUP	NonSmokers	Variance	0.000362	
		COMPOUND SYMMETRY BY GROUP	NonSmokers	CS	0.000129	
Nicotine	nmol/mg Creatinine	COMPOUND SYMMETRY BY GROUP	Smokers	Variance	21.9288	<0.0001
		COMPOUND SYMMETRY BY GROUP	Smokers	CS	51.3661	
		COMPOUND SYMMETRY BY GROUP	NonSmokers	Variance	0.01418	
		COMPOUND SYMMETRY BY GROUP	NonSmokers	CS	0.002096	
Cotinine	nmol/mg Creatinine	COMPOUND SYMMETRY BY GROUP	Smokers	Variance	7.3048	<0.0001

^a P-value to test if the off diagonal terms of the fitted covariance structure are zero based on likelihood ratio test.

Table 14.1.1-2
Covariance Parameter Estimates for Full Model
(Page 3 of 7)

Biomarker	Unit	Covariance Structure	Group	Covariance Parameter	Estimate	P-Value ^a
Cotinine	nmol/mg Creatinine	COMPOUND SYMMETRY BY GROUP	Smokers	CS	36.0831	
		COMPOUND SYMMETRY BY GROUP	NonSmokers	Variance	0.000419	
		COMPOUND SYMMETRY BY GROUP	NonSmokers	CS	0.000235	
Trans-3-hydroxycotinine	nmol/mg Creatinine	COMPOUND SYMMETRY		CS	129.00	<0.0001
		COMPOUND SYMMETRY		Residual	12.2232	
Trans-3-hydroxycotinine-O-glucuronide	nmol/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY		Var(1)	25.5263	<0.0001
		HETEROGENEOUS COMPOUND SYMMETRY		Var(2)	25.0349	
		HETEROGENEOUS COMPOUND SYMMETRY		Var(3)	39.5798	
		HETEROGENEOUS COMPOUND SYMMETRY		CSH	0.8808	
NNAL plus NNAL-gluc	pmol/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(1)	7.4558	<0.0001
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(2)	5.7694	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	CSH	0.7770	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(1)	0.006035	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(2)	0.001646	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	CSH	0.1103	
NNAL	pmol/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(1)	0.6947	<0.0001
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(2)	0.5135	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	CSH	0.8346	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(1)	0.000472	

^a P-value to test if the off diagonal terms of the fitted covariance structure are zero based on likelihood ratio test.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

Table 14.1.1-2
Covariance Parameter Estimates for Full Model
(Page 4 of 7)

Biomarker	Unit	Covariance Structure	Group	Covariance Parameter	Estimate	P-Value ^a
NNAL	pmol/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(2)	0.000887	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	CSH	0.3470	
NNAL-O-glucuronide	pmol/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(1)	3.9548	<0.0001
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(2)	3.6381	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	CSH	0.7014	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(1)	0.005864	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(2)	0.000752	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	CSH	0.007346	
Nicotine-N-glucuronide	nmol/mg Creatinine	COMPOUND SYMMETRY BY GROUP	Smokers	Variance	2.0696	<0.0001
		COMPOUND SYMMETRY BY GROUP	Smokers	CS	4.9177	
		COMPOUND SYMMETRY BY GROUP	NonSmokers	Variance	0.000352	
		COMPOUND SYMMETRY BY GROUP	NonSmokers	CS	0.000027	
Cotinine-N-glucuronide	nmol/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY		Var(1)	36.0590	<0.0001
		HETEROGENEOUS COMPOUND SYMMETRY		Var(2)	43.6516	
		HETEROGENEOUS COMPOUND SYMMETRY		Var(3)	42.4545	
		HETEROGENEOUS COMPOUND SYMMETRY		CSH	0.8898	
Acetonitrile in exhalate	nL/L @20 °C and 1 atm	COMPOUND SYMMETRY		CS	64087072	<0.0001
		COMPOUND SYMMETRY		Residual	1.8022E8	
Carbon monoxide	ppm	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(1)	213.36	<0.0001

^a P-value to test if the off diagonal terms of the fitted covariance structure are zero based on likelihood ratio test.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

Table 14.1.1-2
Covariance Parameter Estimates for Full Model
(Page 5 of 7)

Biomarker	Unit	Covariance Structure	Group	Covariance Parameter	Estimate	P-Value *
Carbon monoxide	ppm	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(2)	242.41	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(3)	205.66	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(4)	211.10	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	CSH	0.8469	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(1)	1.7358	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(2)	2.1103	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(3)	1.9729	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(4)	4.7101	
HDL-cholesterol	mg/dL	HETEROGENEOUS COMPOUND SYMMETRY		CSH	0.1007	
		HETEROGENEOUS COMPOUND SYMMETRY		Var(1)	155.78	<0.0001
		HETEROGENEOUS COMPOUND SYMMETRY		Var(2)	142.63	
		HETEROGENEOUS COMPOUND SYMMETRY		Var(3)	120.25	
LDL-cholesterol	mg/dL	HETEROGENEOUS COMPOUND SYMMETRY		CSH	0.8535	
		HETEROGENEOUS COMPOUND SYMMETRY		CS	696.86	<0.0001
Fibrinogen	mg/dL	COMPOUND SYMMETRY		Residual	243.29	
		COMPOUND SYMMETRY				
		HETEROGENEOUS COMPOUND SYMMETRY		Var(1)	4466.61	<0.0001
		HETEROGENEOUS COMPOUND SYMMETRY		Var(2)	7237.03	
C-reactive protein	mg/dL	HETEROGENEOUS COMPOUND SYMMETRY		Var(3)	4274.13	
		HETEROGENEOUS COMPOUND SYMMETRY		CSH	0.3910	
C-reactive protein	mg/dL	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(1)	0.2552	<0.0001

* P-value to test if the off diagonal terms of the fitted covariance structure are zero based on likelihood ratio test.

Table 14.1.1-2
Covariance Parameter Estimates for Full Model
(Page 6 of 7)

Biomarker	Unit	Covariance Structure	Group	Covariance Parameter	Estimate	P-Value ^a
C-reactive protein	mg/dL	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(2)	0.2548	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(3)	0.2634	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	CSH	0.6722	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(1)	0.5348	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(2)	0.1060	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(3)	0.3859	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	CSH	0.3940	
Malondialdehyde in blood	μmol/L	HETEROGENEOUS COMPOUND SYMMETRY		Var(1)	0.005847	0.0134
		HETEROGENEOUS COMPOUND SYMMETRY		Var(2)	0.007374	
		HETEROGENEOUS COMPOUND SYMMETRY		Var(3)	0.009249	
		HETEROGENEOUS COMPOUND SYMMETRY		CSH	0.1512	
11-Dehydro-thromboxane B2	ng/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(1)	0.2153	<0.0001
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(2)	0.2284	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(3)	0.3177	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	CSH	0.6196	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(1)	0.05542	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(2)	0.09062	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(3)	0.06674	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	CSH	0.6238	
8-Epi-prostaglandin F2α	ng/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(1)	0.8393	<0.0001

^a P-value to test if the off diagonal terms of the fitted covariance structure are zero based on likelihood ratio test.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.1-2
Covariance Parameter Estimates for Full Model
(Page 7 of 7)

Biomarker	Unit	Covariance Structure	Group	Covariance Parameter	Estimate	P-Value *
8-Epi-prostaglandin F2 α	ng/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(2)	1.2294	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(3)	0.5935	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	CSH	0.5814	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(1)	0.1231	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(2)	0.1490	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(3)	0.1293	
Malondialdehyde in urine	nmol/mg Creatinine	HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	CSH	0.6132	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(1)	1.4636	<0.0001
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(2)	0.5791	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	Var(3)	0.3769	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	Smokers	CSH	0.4045	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(1)	1.3309	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(2)	0.6681	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	Var(3)	0.7587	
		HETEROGENEOUS COMPOUND SYMMETRY BY GROUP	NonSmokers	CSH	0.3298	

* P-value to test if the off diagonal terms of the fitted covariance structure are zero based on likelihood ratio test.

PM3006438187

Table 14.1.1-3
Likelihood Ratio Test for No Interaction Between the Full and Reduced Models
(Page 1 of 2)

Biomarker	Unit	Full Model's Likelihood ^a	First Reduced Model's Likelihood ^b	Second Reduced Model's Likelihood ^c	P-value ^d	P-value ^e	P-value ^f
Acetonitrile in blood	(µg/mL)/2	111.6	113.8	129.5	0.0565	---	---
Carboxyhemoglobin	% saturation	630.4	632.6	640.8	0.4077	---	---
3-Aminobiphenyl-Hb adduct	pg/g hemoglobin	696.6	697.2	701.5	0.2898	---	---
4-Aminobiphenyl-Hb adduct	pg/g hemoglobin	1629.1	1629.4	1646.1	0.0020	0.5504	0.0008
Sum of Nicotine and Nicotine metabolites	(nmol/mg Creatinine)/10	-292.9	-291.2	-286.4	0.4853	---	---
Nicotine	nmol/mg Creatinine	708.8	709.4	712.0	0.8715	---	---
Cotinine	nmol/mg Creatinine	-63.2	-61.7	-57.8	0.6156	---	---
Trans-3-hydroxycotinine	nmol/mg Creatinine	2214.7	2216.5	2225.7	0.1398	---	---
Trans-3-hydroxycotinine-O-glucuronide	nmol/mg Creatinine	1633.9	1637.9	1645.7	0.1080	---	---
NNAL plus NNAL-gluc	pmol/mg Creatinine	26.6	27.3	32.5	0.2099	---	---
NNAL	pmol/mg Creatinine	-425.3	-424.3	-417.1	0.0870	---	---
NNAL-O-glucuronide	pmol/mg Creatinine	-40.5	-40.0	-35.9	0.3338	---	---

NOTE: Full Model contains group(smokers, nonsmokers), gender(male, female), week (a subset of Week 1, Week 2, Week 3, and Week 6), and all possible two-way and three-way interaction terms.

First Reduced Model contains group(smokers, nonsmokers), gender(male, female), week (a subset of Week 1, Week 2, Week 3, and Week 6), and all possible two-way interaction terms.

Second Reduced Model contains group(smokers, nonsmokers), gender(male, female), and week (a subset of Week 1, Week 2, Week 3, and Week 6).

^a -2 Log-likelihood from ANOVA for Full Model.

^b -2 Log-likelihood from ANOVA for first Reduced Model.

^c -2 Log-likelihood from ANOVA for second Reduced Model.

^d P-value testing for significance of the two-way and the three-way interaction terms based on the likelihood ratio test (Full model vs. second Reduced Model).

^e P-value testing for significance of the three-way interaction term based on the likelihood ratio test (Full model vs. first Reduced Model).

^f P-value testing for significance of the two-way interaction terms based on the likelihood ratio test (first Reduced Model vs. second Reduced Model).

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

Table 14.1.1-3
Likelihood Ratio Test for No Interaction Between the Full and Reduced Models
(Page 2 of 2)

Biomarker	Unit	Full Model's Likelihood ^a	First Reduced Model's Likelihood ^b	Second Reduced Model's Likelihood ^c	P-value ^d	P-value ^e	P-value ^f
Nicotine-N-glucuronide	nmol/mg Creatinine	-350.3	-349.7	-345.5	0.6859	---	---
Cotinine-N-glucuronide	nmol/mg Creatinine	1842.9	1845.0	1848.8	0.5566	---	---
Acetonitrile in exhalate	nL/l. @20 °C and 1 atm	7356.3	7357.3	7376.5	0.0050	0.5900	0.0018
Carbon monoxide	ppm	2303.1	2305.7	2317.4	0.1595	---	---
HDL-cholesterol	mg/dL	2279.0	2281.2	2285.0	0.5443	---	---
LDL-cholesterol	mg/dL	2986.1	2989.4	2992.5	0.4963	---	---
Fibrinogen	mg/dL	3725.7	3726.5	3729.4	0.8077	---	---
C-reactive protein	mg/dL	421.7	423.8	429.6	0.3448	---	---
Malondialdehyde in blood	μmol/L	-699.3	-636.6	-562.8	<0.0001	<0.0001	---
11-Dehydro-thromboxane B2	ng/mg Creatinine	114.2	115.4	122.2	0.3350	---	---
8-Epi-prostaglandin F2α	ng/mg Creatinine	430.3	430.7	442.0	0.1117	---	---
Malondialdehyde in urine	nmol/mg Creatinine	846.6	848.0	851.5	0.6785	---	---

NOTE: Full Model contains group(smokers, nonsmokers), gender(male,female), week (a subset of Week 1, Week 2, Week 3, and Week 6), and all possible two-way and three-way interaction terms.

First Reduced Model contains group(smokers, nonsmokers), gender(male,female), week (a subset of Week 1, Week 2, Week 3, and Week 6), and all possible two-way interaction terms.

Second Reduced Model contains group(smokers, nonsmokers), gender(male,female), and week (a subset of Week 1, Week 2, Week 3, and Week 6).

^a -2 Log-likelihood from ANOVA for Full Model.

^b -2 Log-likelihood from ANOVA for first Reduced Model.

^c -2 Log-likelihood from ANOVA for second Reduced Model.

^d P-value testing for significance of the two-way and the three-way interaction terms based on the likelihood ratio test (Full model vs. second Reduced Model).

^e P-value testing for significance of the three-way interaction term based on the likelihood ratio test (Full model vs. first Reduced Model).

^f P-value testing for significance of the two-way interaction terms based on the likelihood ratio test (first Reduced Model vs. second Reduced Model).

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.1-4
Overall Analyses: Test for Fixed Effects From Two-Way Interaction Models

Biomarker	Unit	Gender*Group ^a	Group*Week ^b	Gender*Week ^c
4-Aminobiphenyl-Hb adduct	pg/g hemoglobin	0.0025	0.3049	0.0086
Acetonitrile in exhalate	nL/L @20 °C and 1 atm	0.0001	0.9826	0.0959

^a P-value testing for the effect of gender by group using likelihood ratio test.

^b P-value testing for the effect of group by week using likelihood ratio test.

^c P-value testing for the effect of gender by week using likelihood ratio test.

PM3006438190

Table 14.1.1-5
Pairwise Analyses: Least Squares Means and Pairwise Comparisons From Full Models

Biomarker	Unit	Week	Group 1 (# of obs)	Group 2 (# of obs)	Group 1 Mean(SE) ^a	Group 2 Mean(SE) ^a	P-value ^b
Malondialdehyde in blood	μmol/L	1	Female-NonSmokers (35)	Male-NonSmokers (30)	0.46(0.013)	0.43(0.014)	0.0721
		1	Female-Smokers (32)	Female-NonSmokers (35)	0.43(0.014)	0.46(0.013)	0.1037
		1	Female-Smokers (32)	Male-Smokers (18)	0.43(0.014)	0.64(0.018)	<0.0001
		1	Male-Smokers (18)	Male-NonSmokers (30)	0.64(0.018)	0.43(0.014)	<0.0001
		3	Female-NonSmokers (35)	Male-NonSmokers (30)	0.48(0.015)	0.45(0.016)	0.1704
		3	Female-Smokers (29)	Female-NonSmokers (35)	0.48(0.016)	0.48(0.015)	0.8824
		3	Female-Smokers (29)	Male-Smokers (17)	0.48(0.016)	0.64(0.021)	<0.0001
		3	Male-Smokers (17)	Male-NonSmokers (30)	0.64(0.021)	0.45(0.016)	<0.0001
		6	Female-NonSmokers (35)	Male-NonSmokers (30)	0.44(0.016)	0.60(0.018)	<0.0001
		6	Female-Smokers (28)	Female-NonSmokers (35)	0.43(0.018)	0.44(0.016)	0.8486
		6	Female-Smokers (28)	Male-Smokers (14)	0.43(0.018)	0.45(0.026)	0.6404
		6	Male-Smokers (14)	Male-NonSmokers (30)	0.45(0.026)	0.60(0.018)	<0.0001

^a Least squares mean and standard error from ANOVA.

^b P-value for difference between means from ANOVA.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.1-6
Pairwise Analyses: Least Squares Means and Pairwise Comparisons From Two-Way Interaction Models
(Page 1 of 2)

Biomarker	Unit	Group 1 (# of obs)	Group 2 (# of obs)	Group 1 Mean(SE) ^a	Group 2 Mean(SE) ^a	P-value ^b
4-Aminobiphenyl-Hb adduct	pg/g hemoglobin	Female-NonSmokers (70)	Male-NonSmokers (60)	8.42(0.638)	7.60(0.689)	0.3823
		Female-Smokers (59)	Female-NonSmokers (70)	35.83(7.148)	8.42(0.638)	0.0003
		Female-Smokers (59)	Male-Smokers (32)	35.83(7.148)	53.60(8.144)	0.0033
		Male-Smokers (32)	Male-NonSmokers (60)	53.60(8.144)	7.60(0.689)	<0.0001
		Females at Week 1 (66)	Females at Week 6 (63)	18.20(1.788)	26.05(6.876)	0.2669
		Females at Week 1 (66)	Males at Week 1 (48)	18.20(1.788)	25.64(2.325)	0.0135
		Females at Week 6 (63)	Males at Week 6 (44)	26.05(6.876)	35.56(7.270)	0.0024
		Males at Week 1 (48)	Males at Week 6 (44)	25.64(2.325)	35.56(7.270)	0.1630

^a Least squares mean and standard error from ANOVA.

^b P-value for difference between means from ANOVA.

PM3006438192

Table 14.1.1-6
 Pairwise Analyses: Least Squares Means and Pairwise Comparisons From Two-Way Interaction Models
 (Page 2 of 2)

Biomarker	Unit	Group 1 (# of obs)		Group 2 (# of obs)		Group 1 Mean(SE) ^a	Group 2 Mean(SE) ^a	P-value ^b
Acetonitrile in exhalate	nL/L @20 °C and 1 atm	Female-NonSmokers	(105)	Male-NonSmokers	(90)	28173.34(1881.527)	20712.22(2032.282)	0.0082
		Female-Smokers	(89)	Female-NonSmokers	(105)	10351.92(2024.067)	28173.34(1881.527)	<0.0001
		Female-Smokers	(89)	Male-Smokers	(49)	10351.92(2024.067)	20240.32(2713.413)	0.0042
		Male-Smokers	(49)	Male-NonSmokers	(90)	20240.32(2713.413)	20712.22(2032.282)	0.8895

^a Least squares mean and standard error from ANOVA.

^b P-value for difference between means from ANOVA.

Table 14.1.1-7
Least Squares Means and Comparison Results From Additive Models
(Page 1 of 8)

Biomarker	Unit	Group (# of obs)	Mean(SE) ^a	P-value ^b
Acetonitrile in blood	(µg/mL)/2	Female (260)	0.28(0.022)	0.4167
		Male (186)	0.30(0.025)	
		NonSmokers (260)	0.20(0.016)	
		Smokers (186)	0.38(0.034)	<0.0001
		Week 1 (115)	0.25(0.028)	
		Week 2 (113)	0.27(0.024)	
		Week 3 (111)	0.31(0.030)	
Carboxyhemoglobin	% saturation	Week 6 (107)	0.32(0.030)	0.1122
		Female (260)	2.3(0.20)	<0.0001
		Male (186)	2.5(0.20)	
		NonSmokers (260)	0.4(0.02)	
		Smokers (186)	4.4(0.40)	0.0438
		Week 1 (115)	2.4(0.20)	
		Week 2 (114)	2.3(0.20)	
3-Aminobiphenyl-Hb adduct	pg/g hemoglobin	Week 3 (111)	2.5(0.21)	
		Week 6 (106)	2.4(0.20)	
		Female (129)	2.24(0.235)	0.5349
		Male (92)	2.20(0.237)	
		NonSmokers (130)	0.59(0.037)	
		Smokers (91)	3.85(0.466)	<0.0001
		Week 1 (114)	2.22(0.235)	

^a Least squares mean and standard error from ANOVA.

^b P-value based on the likelihood ratio test for difference between group means, gender means, and week means, respectively.

Table 14.1.1-7
 Least Squares Means and Comparison Results From Additive Models
 (Page 2 of 8)

Biomarker	Unit	Group (# of obs)	Mean(SE) ^a	P-value ^b
3-Aminobiphenyl-Hb adduct	pg/g hemoglobin	Week 6 (107)	2.22(0.238)	
Sum of Nicotine and Nicotine metabolites	(nmol/mg Creatinine)/10	Female (197)	3.487(0.3047)	0.1359
		Male (143)	3.493(0.3047)	
		NonSmokers (195)	0.008(0.0020)	<0.0001
		Smokers (145)	6.972(0.6093)	
		Week 1 (115)	3.489(0.3047)	0.2460
		Week 2 (114)	3.493(0.3047)	
		Week 3 (111)	3.488(0.3047)	
Nicotine	nmol/mg Creatinine	Female (197)	4.688(0.5446)	0.2495
		Male (143)	4.712(0.5447)	
		NonSmokers (195)	0.024(0.0103)	<0.0001
		Smokers (145)	9.376(1.0891)	
		Week 1 (115)	4.697(0.5447)	0.3956
		Week 2 (114)	4.716(0.5447)	
		Week 3 (111)	4.687(0.5447)	
Cotinine	nmol/mg Creatinine	Female (197)	4.463(0.4432)	0.3222
		Male (143)	4.468(0.4432)	
		NonSmokers (195)	0.014(0.0024)	<0.0001
		Smokers (145)	8.918(0.8864)	
		Week 1 (115)	4.465(0.4432)	0.4290

^a Least squares mean and standard error from ANOVA.

^b P-value based on the likelihood ratio test for difference between group means, gender means, and week means, respectively.

Table 14.1.1-7
Least Squares Means and Comparison Results From Additive Models
(Page 3 of 8)

Biomarker	Unit	Group (# of obs)	Mean(SE) ^a	P-value ^b
Cotinine	nmol/mg Creatinine	Week 2 (114)	4.468(0.4432)	
		Week 3 (111)	4.464(0.4432)	
Trans-3-hydroxycotinine	nmol/mg Creatinine	Female (197)	14.098(1.4246)	0.2081
		Male (143)	11.300(1.7036)	
		NonSmokers (195)	0.000(1.4469)	<0.0001
		Smokers (145)	25.479(1.6774)	
		Week 1 (115)	12.232(1.1456)	0.1193
		Week 2 (114)	13.207(1.1464)	
		Week 3 (111)	12.658(1.1485)	
Trans-3-hydroxycotinine-O-glucuronide	nmol/mg Creatinine	Female (183)	4.321(0.6076)	0.9130
		Male (133)	4.420(0.7117)	
		NonSmokers (173)	0.285(0.6126)	<0.0001
		Smokers (143)	8.456(0.7047)	
		Week 1 (102)	4.328(0.4794)	0.2240
		Week 2 (108)	4.136(0.4744)	
		Week 3 (106)	4.648(0.5811)	
NNAL plus NNAL-gluc	pmol/mg Creatinine	Female (131)	1.775(0.1747)	0.0257
		Male (94)	1.754(0.1748)	
		NonSmokers (130)	0.050(0.0057)	<0.0001
		Smokers (95)	3.479(0.3493)	

^a Least squares mean and standard error from ANOVA.

^b P-value based on the likelihood ratio test for difference between group means, gender means, and week means, respectively.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

Table 14.1.1-7
Least Squares Means and Comparison Results From Additive Models
(Page 4 of 8)

Biomarker	Unit	Group (# of obs)	Mean(SE) ^a	P-value ^b
NNAL plus NNAL-gluc	pmol/mg Creatinine	Week 1 (114)	1.764(0.1748)	0.8832
		Week 3 (111)	1.765(0.1747)	
NNAL	pmol/mg Creatinine	Female (131)	0.569(0.0543)	0.0001
		Male (95)	0.549(0.0544)	
		NonSmokers (130)	0.044(0.0026)	<0.0001
		Smokers (96)	1.074(0.1086)	
		Week 1 (115)	0.555(0.0543)	0.0273
		Week 3 (111)	0.563(0.0543)	
NNAL-O-glucuronide	pmol/mg Creatinine	Female (128)	1.211(0.1301)	0.3451
		Male (91)	1.207(0.1301)	
		NonSmokers (124)	0.009(0.0053)	<0.0001
		Smokers (93)	2.409(0.2600)	
		Week 1 (110)	1.213(0.1302)	0.5288
		Week 3 (109)	1.206(0.1300)	
Nicotine-N-glucuronide	nmol/mg Creatinine	Female (194)	1.585(0.1707)	0.1159
		Male (138)	1.590(0.1707)	
		NonSmokers (190)	0.003(0.0015)	<0.0001
		Smokers (142)	3.172(0.3415)	
		Week 1 (111)	1.586(0.1707)	0.4038
		Week 2 (111)	1.590(0.1707)	

^a Least squares mean and standard error from ANOVA.

^b P-value based on the likelihood ratio test for difference between group means, gender means, and week means, respectively.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

Table 14.1.1-7
Least Squares Means and Comparison Results From Additive Models
(Page 5 of 8)

Biomarker	Unit	Group (# of obs)	Mean(SE) ^a	P-value ^b
Nicotine-N-glucuronide	nmol/mg Creatinine	Week 3 (110)	1.586(0.1707)	
Cotinine-N-glucuronide	nmol/mg Creatinine	Female (197)	7.323(0.7511)	0.2199
		Male (143)	5.901(0.8943)	
		NonSmokers (195)	0.004(0.7628)	<0.0001
		Smokers (145)	13.219(0.8805)	
		Week 1 (115)	6.547(0.5793)	0.9235
		Week 2 (114)	6.641(0.6397)	
		Week 3 (111)	6.647(0.6269)	
Carbon monoxide	ppm	Female (260)	15.5(0.98)	<0.0001
		Male (187)	16.8(0.99)	
		NonSmokers (260)	5.6(0.11)	<0.0001
		Smokers (187)	26.7(1.96)	
		Week 1 (115)	16.3(0.99)	0.0004
		Week 2 (114)	15.7(1.00)	
		Week 3 (111)	15.8(0.99)	
		Week 6 (107)	16.9(1.01)	
HDL-cholesterol	mg/dL	Female (194)	54(1.4)	<0.0001
		Male (139)	44(1.6)	
		NonSmokers (195)	54(1.4)	<0.0001
		Smokers (138)	45(1.6)	

^a Least squares mean and standard error from ANOVA.

^b P-value based on the likelihood ratio test for difference between group means, gender means, and week means, respectively.

Table 14.1.1-7
Least Squares Means and Comparison Results From Additive Models
(Page 6 of 8)

Biomarker	Unit	Group (# of obs)	Mean(SE) ^a	P-value ^b
HDL-cholesterol	mg/dL	Week 1 (115)	50(1.2)	0.1323
		Week 3 (111)	49(1.2)	
		Week 6 (107)	49(1.1)	
LDL-cholesterol	mg/dL	Female (192)	116(3.4)	0.7073
		Male (136)	114(4.1)	
		NonSmokers (193)	111(3.5)	
		Smokers (135)	119(4.1)	0.1364
		Week 1 (111)	117(2.9)	
		Week 3 (110)	111(3.0)	
		Week 6 (107)	115(3.0)	0.0116
Fibrinogen	mg/dL	Female (193)	300(6.8)	<0.0001
		Male (138)	242(8.1)	
		NonSmokers (193)	251(6.9)	
		Smokers (138)	291(8.1)	0.0003
		Week 1 (115)	276(6.4)	
		Week 3 (111)	271(8.2)	
		Week 6 (105)	266(6.5)	0.3937
C-reactive protein	mg/dL	Female (194)	0.425(0.0486)	0.0020
		Male (139)	0.202(0.0567)	
		NonSmokers (195)	0.246(0.0467)	

^a Least squares mean and standard error from ANOVA.

^b P-value based on the likelihood ratio test for difference between group means, gender means, and week means, respectively.

Table 14.1.1-7
Least Squares Means and Comparison Results From Additive Models
(Page 7 of 8)

Biomarker	Unit	Group (# of obs)	Mean(SE) ^a	P-value ^b
C-reactive protein	mg/dL	Smokers (138)	0.382(0.0652)	0.5175
		Week 1 (115)	0.318(0.0528)	
		Week 3 (111)	0.284(0.0416)	
		Week 6 (107)	0.339(0.0529)	
11-Dihydro-thromboxane B2	ng/mg Creatinine	Female (196)	0.936(0.0392)	0.0024
		Male (143)	0.776(0.0445)	
		NonSmokers (195)	0.703(0.0283)	
		Smokers (144)	1.009(0.0607)	0.0114
		Week 1 (115)	0.812(0.0347)	
		Week 2 (114)	0.876(0.0385)	
		Week 3 (110)	0.881(0.0378)	
8-Epi-prostaglandin F2 α	ng/mg Creatinine	Female (196)	1.631(0.0652)	0.0391
		Male (143)	1.472(0.0721)	
		NonSmokers (195)	1.101(0.0392)	
		Smokers (144)	2.001(0.1087)	0.0242
		Week 1 (115)	1.500(0.0612)	
		Week 2 (114)	1.610(0.0653)	
		Week 3 (110)	1.543(0.0603)	
Malondialdehyde in urine	nmol/mg Creatinine	Female (197)	1.854(0.0809)	0.0105
		Male (143)	1.541(0.0948)	

^a Least squares mean and standard error from ANOVA.

^b P-value based on the likelihood ratio test for difference between group means, gender means, and week means, respectively.

Table 14.1.1-7
Least Squares Means and Comparison Results From Additive Models
(Page 8 of 8)

Biomarker	Unit	Group (# of obs)	Mean(SE) ^a	P-value ^b
Malondialdehyde in urine	nmol/mg Creatinine	NonSmokers (195)	1.706(0.0862)	0.8866
		Smokers (145)	1.689(0.0901)	
		Week 1 (115)	1.797(0.1111)	
		Week 2 (114)	1.705(0.0755)	
		Week 3 (111)	1.591(0.0698)	

^a Least squares mean and standard error from ANOVA.

^b P-value based on the likelihood ratio test for difference between group means, gender means, and week means, respectively.

Table 14.1.1-8
Intra and Inter Subject Variabilities
(Page 1 of 6)

Biomarker	Unit	Group	Subject Variability	Lsmean	Variance	Standard Deviation	% CV
Acetonitrile in blood	µg/mL	NonSmokers	Intra	0.20	0.006	0.080	40.8
		NonSmokers	Inter	0.20	0.053	0.230	116.7
		Smokers	Intra	0.44	0.024	0.156	35.4
		Smokers	Inter	0.44	0.154	0.392	89.2
Carboxyhemoglobin	% saturation	NonSmokers	Intra	0.4	0.02	0.13	30.9
		NonSmokers	Inter	0.4	0.08	0.29	68.6
		Smokers	Intra	4.3	7.86	2.80	64.5
		Smokers	Inter	4.3	9.05	3.01	69.3
3-Aminobiphenyl-Hb adduct	pg/g hemoglobin	NonSmokers	Intra	0.59	0.000	0.000	0.0
		NonSmokers	Inter	0.59	0.185	0.430	72.9
		Smokers	Intra	3.95	9.562	3.092	78.4
		Smokers	Inter	3.95	10.399	3.225	81.7
4-Aminobiphenyl-Hb adduct	pg/g hemoglobin	NonSmokers	Intra	8.01	11.904	3.450	43.1
		NonSmokers	Inter	8.01	16.587	4.073	50.8
		Smokers	Intra	38.16	343.544	18.535	48.6
		Smokers	Inter	38.16	397.631	19.941	52.3
Sum of Nicotine and Nicotine metabolites	(nmol/mg Creatinine)/10	NonSmokers	Intra	0.008	0.0001	0.0114	137.2
		NonSmokers	Inter	0.008	0.0005	0.0222	267.3
		Smokers	Intra	6.786	17.5734	4.1921	61.8

Note: Negative estimates were reset to 0. Negative estimate in Mixed procedure is an indication of small variance estimate.
Model includes group, gender, week, and all 2-way and 3-way interactions. Compound symmetry covariance structure by group was used to extract inter-subject variability and intra-subject variability.
Subject 15 data was excluded from Week 6 in the above analysis. Subject had extremely high values for 3-Aminobiphenyl-Hb adduct and 4-Aminobiphenyl-Hb adduct at Week 6.

Table 14.1.1-8
Intra and Inter Subject Variabilities
(Page 2 of 6)

Biomarker	Unit	Group	Subject Variability	Lsmean	Variance	Standard Deviation	% CV
Sum of Nicotine and Nicotine metabolites	(nmol/mg Creatinine)/10	Smokers	Inter	6.786	19.1395	4.3749	64.5
Nicotine	nmol/mg Creatinine	NonSmokers	Intra	0.024	0.0021	0.0458	191.3
		NonSmokers	Inter	0.024	0.0163	0.1276	533.1
		Smokers	Intra	9.315	51.3661	7.1670	76.9
		Smokers	Inter	9.315	73.2949	8.5612	91.9
Cotinine	nmol/mg Creatinine	NonSmokers	Intra	0.014	0.0002	0.0153	108.2
		NonSmokers	Inter	0.014	0.0007	0.0256	180.5
		Smokers	Intra	8.721	36.0831	6.0069	68.9
		Smokers	Inter	8.721	43.3879	6.5870	75.5
Trans-3-hydroxycotinine	nmol/mg Creatinine	NonSmokers	Intra	0.027	0.0011	0.0325	119.4
		NonSmokers	Inter	0.027	0.0022	0.0468	172.0
		Smokers	Intra	24.942	296.8453	17.2292	69.1
		Smokers	Inter	24.942	325.7711	18.0491	72.4
Trans-3-hydroxycotinine-O-glucuronide	nmol/mg Creatinine	NonSmokers	Intra	0.007	0.0001	0.0098	146.1
		NonSmokers	Inter	0.007	0.0002	0.0137	204.4
		Smokers	Intra	8.968	58.6311	7.6571	85.4
		Smokers	Inter	8.968	67.2931	8.2032	91.5
NNAL plus NNAL-gluc	pmol/mg Creatinine	NonSmokers	Intra	0.051	0.0003	0.0186	36.7

Note: Negative estimates were reset to 0. Negative estimate in Mixed procedure is an indication of small variance estimate.
Model includes group, gender, week, and all 2-way and 3-way interactions. Compound symmetry covariance structure by group was used to extract inter-subject variability and intra-subject variability.
Subject 15 data was excluded from Week 6 in the above analysis. Subject had extremely high values for 3-Aminobiphenyl-Hb adduct and 4-Aminobiphenyl-Hb adduct at Week 6.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

Table 14.1.1-8
Intra and Inter Subject Variabilities
(Page 3 of 6)

Biomarker	Unit	Group	Subject Variability	Lsmean	Variance	Standard Deviation	% CV
NNAL plus NNAL-gluc	pmol/mg Creatinine	NonSmokers	Inter	0.051	0.0038	0.0620	122.0
		Smokers	Intra	3.328	5.1728	2.2744	68.3
		Smokers	Inter	3.328	6.6883	2.5862	77.7
NNAL	pmol/mg Creatinine	NonSmokers	Intra	0.044	0.0002	0.0150	34.0
		NonSmokers	Inter	0.044	0.0007	0.0261	59.1
		Smokers	Intra	0.998	0.5079	0.7127	71.4
		Smokers	Inter	0.998	0.6128	0.7828	78.5
NNAL-O-glucuronide	pmol/mg Creatinine	NonSmokers	Intra	0.009	0.0000	0.0039	41.8
		NonSmokers	Inter	0.009	0.0034	0.0586	621.1
		Smokers	Intra	2.330	2.6729	1.6349	70.2
		Smokers	Inter	2.330	3.8092	1.9517	83.8
Nicotine-N-glucuronide	nmol/mg Creatinine	NonSmokers	Intra	0.003	0.0000	0.0052	166.7
		NonSmokers	Inter	0.003	0.0004	0.0195	622.0
		Smokers	Intra	3.056	4.9177	2.2176	72.6
		Smokers	Inter	3.056	6.9874	2.6434	86.5
Cotinine-N-glucuronide	nmol/mg Creatinine	NonSmokers	Intra	0.009	0.0002	0.0143	163.0
		NonSmokers	Inter	0.009	0.0004	0.0199	226.0
		Smokers	Intra	12.938	82.8946	9.1046	70.4
		Smokers	Inter	12.938	93.7510	9.6825	74.8

Note: Negative estimates were reset to 0. Negative estimate in Mixed procedure is an indication of small variance estimate.
Model includes group, gender, week, and all 2-way and 3-way interactions. Compound symmetry covariance structure by group was used to extract inter-subject variability and intra-subject variability.
Subject 15 data was excluded from Week 6 in the above analysis. Subject had extremely high values for 3-Aminobiphenyl-Hb adduct and 4-Aminobiphenyl-Hb adduct at Week 6.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

Table 14.1.1-8
Intra and Inter Subject Variabilities
(Page 4 of 6)

Biomarker	Unit	Group	Subject Variability	Lsmean	Variance	Standard Deviation	% CV
Acetonitrile in exhalate	nL/L @20 °C and 1 atm	NonSmokers	Intra	24442.78	41423258	6436.090	26.3
		NonSmokers	Inter	24442.78	2.6356E8	16234.39	66.4
		Smokers	Intra	15440.00	1.0294E8	10145.70	65.7
		Smokers	Inter	15440.00	2.2047E8	14848.26	96.2
Carbon monoxide	ppm	NonSmokers	Intra	5.6	0.26	0.51	9.1
		NonSmokers	Inter	5.6	2.64	1.62	28.9
		Smokers	Intra	26.0	185.11	13.61	52.2
		Smokers	Inter	26.0	219.04	14.80	56.8
HDL-cholesterol	mg/dL	NonSmokers	Intra	53	124.2	11.1	20.8
		NonSmokers	Inter	53	146.2	12.1	22.6
		Smokers	Intra	46	112.4	10.6	23.2
		Smokers	Inter	46	132.1	11.5	25.2
LDL-cholesterol	mg/dL	NonSmokers	Intra	110	723.4	26.9	24.4
		NonSmokers	Inter	110	979.3	31.3	28.3
		Smokers	Intra	119	662.0	25.7	21.6
		Smokers	Inter	119	888.6	29.8	25.0
Fibrinogen	mg/dL	NonSmokers	Intra	251	1553.5	39.4	15.7
		NonSmokers	Inter	251	4332.3	65.8	26.2
		Smokers	Intra	292	2756.2	52.5	18.0

Note: Negative estimates were reset to 0. Negative estimate in Mixed procedure is an indication of small variance estimate.
Model includes group, gender, week, and all 2-way and 3-way interactions. Compound symmetry covariance structure by group was used to extract inter-subject variability and intra-subject variability.
Subject 15 data was excluded from Week 6 in the above analysis. Subject had extremely high values for 3-Aminobiphenyl-Hb adduct and 4-Aminobiphenyl-Hb adduct at Week 6.

Table 14.1.1-8
Intra and Inter Subject Variabilities
(Page 5 of 6)

Biomarker	Unit	Group	Subject Variability	Lsmean	Variance	Standard Deviation	% CV
Fibrinogen	mg/dL	Smokers	Inter	292	6791.5	82.4	28.3
C-reactive protein	mg/dL	NonSmokers	Intra	0.274	0.0985	0.3138	114.7
		NonSmokers	Inter	0.274	0.3320	0.5762	210.6
		Smokers	Intra	0.393	0.1727	0.4156	105.8
		Smokers	Inter	0.393	0.2581	0.5080	129.3
Malondialdehyde in blood	μmol/L	NonSmokers	Intra	0.48	0.001	0.031	6.6
		NonSmokers	Inter	0.48	0.007	0.086	18.1
		Smokers	Intra	0.51	0.001	0.029	5.8
		Smokers	Inter	0.51	0.007	0.086	16.9
11-Dehydro-thromboxane B2	ng/mg Creatinine	NonSmokers	Intra	0.705	0.0435	0.2087	29.6
		NonSmokers	Inter	0.705	0.0709	0.2663	37.8
		Smokers	Intra	1.023	0.1527	0.3908	38.2
		Smokers	Inter	1.023	0.2505	0.5005	48.9
8-Epi-prostaglandin F2α	ng/mg Creatinine	NonSmokers	Intra	1.101	0.0819	0.2863	26.0
		NonSmokers	Inter	1.101	0.1339	0.3659	33.2
		Smokers	Intra	2.009	0.5161	0.7184	35.8
		Smokers	Inter	2.009	0.9041	0.9508	47.3
Malondialdehyde in urine	nmol/mg Creatinine	NonSmokers	Intra	1.683	0.2849	0.5338	31.7

Note: Negative estimates were reset to 0. Negative estimate in Mixed procedure is an indication of small variance estimate.
Model includes group, gender, week, and all 2-way and 3-way interactions. Compound symmetry covariance structure by group was used to extract inter-subject variability and intra-subject variability.
Subject 15 data was excluded from Week 6 in the above analysis. Subject had extremely high values for 3-Aminobiphenyl-Hb adduct and 4-Aminobiphenyl-Hb adduct at Week 6.

Table 14.1.1-8
Intra and Inter Subject Variabilities
(Page 6 of 6)

Biomarker	Unit	Group	Subject Variability	Lsmean	Variance	Standard Deviation	% CV
Malondialdehyde in urine	nmol/mg Creatinine	NonSmokers	Inter	1.683	0.9155	0.9568	56.9
		Smokers	Intra	1.717	0.3086	0.5556	32.4
		Smokers	Inter	1.717	0.8322	0.9123	53.1

Note: Negative estimates were reset to 0. Negative estimate in Mixed procedure is an indication of small variance estimate.
Model includes group, gender, week, and all 2-way and 3-way interactions. Compound symmetry covariance structure by group was used to extract inter-subject variability and intra-subject variability.
Subject 15 data was excluded from Week 6 in the above analysis. Subject had extremely high values for 3-Aminobiphenyl-Hb adduct and 4-Aminobiphenyl-Hb adduct at Week 6.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

14.1.2 Time Effect

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.2-1
Likelihood Ratio Test For Time Effect
(Page 1 of 2)

Biomarker	Unit	Full Model's Likelihood ^a	Reduced Model's Likelihood ^b	P-value ^c
Acetonitrile in blood	(µg/mL)/2	111.6	128.5	0.1530
Carboxyhemoglobin	% saturation	630.4	648.7	0.1056
3-Aminobiphenyl-Hb adduct	pg/g hemoglobin	696.6	699.1	0.6414
4-Aminobiphenyl-Hb adduct	pg/g hemoglobin	1629.1	1650.7	0.0002
Sum of Nicotine and Nicotine metabolites	(nmol/mg Creatinine)/10	-292.9	-284.8	0.4250
Nicotine	nmol/mg Creatinine	708.8	713.8	0.7619
Cotinine	nmol/mg Creatinine	-63.2	-56.7	0.5946
Trans-3-hydroxycotinine	nmol/mg Creatinine	2214.7	2227.7	0.1137
Trans-3-hydroxycotinine-O-glucuronide	nmol/mg Creatinine	1633.9	1648.6	0.0640
NNAL plus NNAL-gluc	pmol/mg Creatinine	26.6	29.9	0.5182
NNAL	pmol/mg Creatinine	-425.3	-418.0	0.1249
NNAL-O-glucuronide	pmol/mg Creatinine	-40.5	-36.8	0.4456

NOTE: Full Model contains group(smokers, nonsmokers), gender(male,female), week (a subset of Week 1, Week 2, Week 3, and Week 6), and all possible two-way and three-way interaction terms.

Reduced Model contains group(smokers, nonsmokers), gender(male,female), and group by gender interaction terms.

^a -2 Log-likelihood from ANOVA for Full Model.

^b -2 Log-likelihood from ANOVA for Reduced Model.

^c P-value testing for significance of time based on the likelihood ratio test (Full model vs. Reduced Model).

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

Final Draft: 22 October 2003

Page 240 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.2-1
Likelihood Ratio Test For Time Effect
(Page 2 of 2)

Biomarker	Unit	Full Model's Likelihood ^a	Reduced Model's Likelihood ^b	P-value ^c
Nicotine-N-glucuronide	nmol/mg Creatinine	-350.3	-345.2	0.7418
Cotinine-N-glucuronide	nmol/mg Creatinine	1842.9	1846.7	0.8746
Acetonitrile in exhalate	nL/L @20 °C and 1 atm	7356.3	7364.1	0.4491
Carbon monoxide	ppm	2303.1	2335.5	0.0012
HDL-cholesterol	mg/dL	2279.0	2285.7	0.5668
LDL-cholesterol	mg/dL	2986.1	3000.9	0.0644
Fibrinogen	mg/dL	3725.7	3731.2	0.6947
C-reactive protein	mg/dL	421.7	430.6	0.3524
Malondialdehyde in blood	μmol/L	-699.3	-601.8	<0.0001
11-Dehydro-thromboxane B2	ng/mg Creatinine	114.2	131.0	0.0322
8-Epi-prostaglandin F2α	ng/mg Creatinine	430.3	447.4	0.0295
Malondialdehyde in urine	nmol/mg Creatinine	846.6	855.2	0.3755

NOTE: Full Model contains group(smokers, nonsmokers), gender(male,female), week (a subset of Week 1, Week 2, Week 3, and Week 6), and all possible two-way and three-way interaction terms.
Reduced Model contains group(smokers, nonsmokers), gender(male,female), and group by gender interaction terms.

^a -2 Log-likelihood from ANOVA for Full Model.

^b -2 Log-likelihood from ANOVA for Reduced Model.

^c P-value testing for significance of time based on the likelihood ratio test (Full model vs. Reduced Model).

PM3006438210

Final Draft: 22 October 2003

Page 241 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

14.1.3 Dose Response Modeling

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-1
Variables Considered in Exposure-Response Modeling
(Page 1 of 2)

Variable	Source	Type	Definition ^a
Self-exposure	Questionnaire/Survey	Continuous	3 Day (Week 1 Survey) or 3 Month (Enrollment Questionnaire) Exposure From Cigarettes
Age (years)	Case Report Form	Continuous	Age at Enrollment
Alcohol Use	Questionnaire	Categorical	A Value of 1 for the Use of Alcohol in the Past 3 Months and 0 Otherwise
Body Mass Index (kg/m ²)	Case Report Form	Continuous	Body Mass Index at Screening
Diastolic Blood Pressure (mmHg)	Case Report Form	Continuous	Diastolic Blood Pressure at Enrollment or Week 1
Exercise	Questionnaire	Categorical	A Value of 1 for Exercise at Least Twice a Month and 0 Otherwise
Use of Air Filtration Device	Questionnaire	Categorical	A Value of 1 for the Use of Air Filtration Device at Home and 0 Otherwise
Type of Heating System At Home	Questionnaire	Categorical	A Value of 1 for the Use of Gas in Home and 0 Otherwise
Exposure to Chemicals and/or Engine Exhaust at the Job	Questionnaire	Categorical	A Value of 1 for Being Exposed in the Past 3 Months and 0 Otherwise
Job Status	Questionnaire	Categorical	A Value of 1 for Being Employed in at Least Two Jobs in the Past 3 Months and 0 Otherwise
Marital Status	Questionnaire	Categorical	A Value of 1 for Currently or Formerly Being Married and 0 Otherwise
NAT2 Phenotyping	Labs	Categorical	A Value of 1 for a Fast Phenotyping for NAT2 and 0 Otherwise

^a Calculation of exposure variables are provided in the report.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-1
Variables Considered in Exposure-Response Modeling
(Page 2 of 2)

Variable	Source	Type	Definition ^a
Exposure to Cigarette Smoke From Visitors to Subject's Home	Questionnaire/Survey	Continuous	3 Day or 3 Month Exposure to Cigarette Smoke
Exposure to Cigarette Smoke in Places (Bar, Restaurant, etc)	Questionnaire/Survey	Continuous	3 Day or 3 Month Exposure to Cigarette Smoke
Pulse (bpm)	Case Report Form	Continuous	Heart Rate at Enrollment or Week 1
Servings High in Fat (per week)	Questionnaire	Continuous	Total Servings per Week at Enrollment
Gender	Case Report Form	Categorical	A Value of 1 for Males and 0 Otherwise
Exposure to Cigarette Smoke From Spouse at Home	Questionnaire/Survey	Continuous	3 Day or 3 Month Exposure to Cigarette Smoke
Systolic Blood Pressure (mmHg)	Case Report Form	Continuous	Systolic Blood Pressure at Enrollment or Week 1
Triglycerides (mmol/L)	Labs	Continuous	Triglyceride Values at Enrollment or Week 1
Exposure to Cigarette Smoke in Vehicles	Questionnaire/Survey	Continuous	3 Day or 3 Month Exposure to Cigarette Smoke
Use of Vitamins	Case Report Form	Categorical	A Value of 1 for the Use of Vitamins and 0 Otherwise
Exposure to Cigarette Smoke at the Work Place	Questionnaire/Survey	Continuous	3 Day or 3 Month Exposure to Cigarette Smoke
CYP1A2 Phenotyping	Labs	Categorical	A Value of 1 for Good Phenotyping for CYP1A2 and 0 Otherwise

^a Calculation of exposure variables are provided in the report.

PM3006438213

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-2
Biomarkers Used in Exposure-Response Modeling
(Page 1 of 2)

Biomarker	Unit	Half-Lives Assumed (Days)		Phase	Response
Acetonitrile in blood	(ng/mL)/2	<= 3		Gas	Carbon Monoxide
Carboxyhemoglobin	% saturation	<= 3		Gas	Carbon Monoxide
3-Aminobiphenyl-Hb adducts	pg/g hemoglobin		> 3	Particulate	Tar
4-Aminobiphenyl-Hb adducts	pg/g hemoglobin		> 3	Particulate	Tar
Sum of Nicotine and Nicotine metabolites	nmol/mg Creatinine	<= 3	> 3	Particulate	Nicotine
Nicotine	nmol/mg Creatinine	<= 3	> 3	Particulate	Nicotine
Cotinine	nmol/mg Creatinine	<= 3	> 3	Particulate	Nicotine
<i>trans</i> -3-hydroxycotinine	nmol/mg Creatinine	<= 3		Particulate	Nicotine
<i>trans</i> -3-hydroxycotinine- <i>O</i> -glucuronide	nmol/mg Creatinine	<= 3		Particulate	Nicotine
NNAL plus NNAL-gluc	pmol/mg Creatinine		> 3	Particulate	Tar
NNAL	pmol/mg Creatinine		> 3	Particulate	Tar
NNAL- <i>O</i> -glucuronide	pmol/mg Creatinine		> 3	Particulate	Tar
Nicotine- <i>N</i> -glucuronide	nmol/mg Creatinine	<= 3	> 3	Particulate	Nicotine

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

Final Draft: 22 October 2003

Page 245 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-2
Biomarkers Used in Exposure-Response Modeling
(Page 2 of 2)

Biomarker	Unit	Half-Lives Assumed (Days)		Phase	Response
Cotinine- <i>N</i> -glucuronide	nmol/mg Creatinine	<= 3	> 3	Particulate	Nicotine
Carbon monoxide	ppm	<= 3		Gas	Carbon Monoxide

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-3
Parameter Estimates for Biomarkers of Exposure with Half-Life Less Than or Equal to 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 1 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
Acetonitrile in blood	ng/mL	Intercept	-0.196336	0.3924570	0.5805
		Self-exposure	0.000491	0.0004605	0.3376
		Age	-0.012003	0.0081592	0.1066
		Exercise	-0.250411	0.1823234	0.1417
		Gender	0.445693	0.1733485	0.0076

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-3
Parameter Estimates for Biomarkers of Exposure with Half-Life Less Than or Equal to 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 2 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
Carboxyhemoglobin	% saturation	Intercept	0.241380	0.4591156	0.5765
		Self-exposure	0.001215	0.0004515	0.0075
		NAT2 Phenotyping	0.278263	0.1442476	0.0495
		Exposure to Cigarette Smoke From Visitors to Subject's Home	0.002559	0.0014239	0.0408
		Exposure to Cigarette Smoke From Spouse at Home	0.001539	0.0007894	0.0254
		Systolic Blood Pressure	-0.010957	0.0037348	0.0015
		Triglycerides	0.115723	0.0649646	0.0869
		CYP1A2 Phenotyping	0.221441	0.1361793	0.1116 ^a

^a Wald p-value was shown instead of quasi-likelihood p-value due to unresolved convergence problems.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-3
Parameter Estimates for Biomarkers of Exposure with Half-Life Less Than or Equal to 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 3 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
Sum of Nicotine and Nicotine metabolites	nmol/mg Creatinine	Intercept	0.855702	0.6892584	0.1934
		Self-exposure	0.004615	0.0008907	<0.0001
		Diastolic Blood Pressure	-0.029437	0.0102817	0.0032
		Exposure to Cigarette Smoke in Places	0.141714	0.0453914	0.0003
		Servings High in Fat	-0.013061	0.0048848	0.0251
		Exposure to Cigarette Smoke From Spouse at Home	0.002645	0.0009809	0.0003
		Triglycerides	0.223302	0.0830583	0.0056
		CYP1A2 Phenotyping	0.297173	0.1488958	0.0470
		Interaction between Self-exposure and Exposure to Cigarette Smoke in Places	-0.000604	0.0001788	0.0004

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-3
Parameter Estimates for Biomarkers of Exposure with Half-Life Less Than or Equal to 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 4 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
Nicotine	nmol/mg Creatinine	Intercept	-1.497743	0.2514473	<0.0001
		Self-exposure	0.001604	0.0005094	0.0022
		Age	0.014508	0.0060193	0.0175
		NAT2 Phenotyping	0.273895	0.1426963	0.0551
		Exposure to Cigarette Smoke From Visitors to Subject's Home	0.001762	0.0011343	0.0910
		Servings High in Fat	-0.007038	0.0050789	0.0001
		Exposure to Cigarette Smoke From Spouse at Home	0.002005	0.0007854	0.0036

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-3
Parameter Estimates for Biomarkers of Exposure with Half-Life Less Than or Equal to 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 5 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
Cotinine	nmol/mg Creatinine	Intercept	-0.061131	0.4064676	0.8832
		Self-exposure	0.001643	0.0005350	0.0011
		Age	0.009740	0.0061555	0.1147
		Body Mass Index	-0.020746	0.0089445	0.0266
		Job Status	-0.443813	0.1656637	0.0043
		Servings High in Fat	-0.011072	0.0047884	0.0199
		Exposure to Cigarette Smoke From Spouse at Home	0.002641	0.0008547	<0.0001
		CYP1A2 Phenotyping	0.250673	0.1356350	0.0694

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-3
Parameter Estimates for Biomarkers of Exposure with Half-Life Less Than or Equal to 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 6 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
Trans-3-hydroxycotinine	nmol/mg Creatinine	Intercept	-0.372936	0.4085448	0.3648
		Self-exposure	0.001811	0.0005995	0.0029
		Alcohol Use	0.320910	0.1870219	0.1083
		Body Mass Index	-0.045218	0.0100594	<0.0001
		Use of Air Filtration Device	0.197364	0.1706074	0.0024
		Type of Heating System At Home	0.414330	0.1570902	0.0124
		Exposure to Cigarette Smoke in Places	0.066737	0.0213646	0.0013
		Servings High in Fat	-0.017007	0.0053383	0.0024
		Gender	-0.425968	0.1328169	0.0016
		Exposure to Cigarette Smoke From Spouse at Home	0.002241	0.0008791	0.0013
		Triglycerides	0.259458	0.0749124	0.0006
		Exposure to Cigarette Smoke at the Work Place	0.081292	0.0448428	0.0407
		CYP1A2 Phenotyping	0.458212	0.1528545	0.0025

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-3
Parameter Estimates for Biomarkers of Exposure with Half-Life Less Than or Equal to 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 7 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
Trans-3-hydroxycotinine-O-glucuronide	nmol/mg Creatinine	Intercept	-0.551557	0.4265084	0.1890
		Self-exposure	0.002307	0.0004655	<0.0001
		Age	0.026152	0.0066709	0.0001
		Use of Air Filtration Device	0.284836	0.1327536	0.0036
		Marital Status	-0.512928	0.1454429	0.0005
		Exposure to Cigarette Smoke in Places	0.054133	0.0163600	0.0005
		Servings High in Fat	-0.009416	0.0038399	0.0190 ^a
		Exposure to Cigarette Smoke From Spouse at Home	0.001499	0.0006623	0.0146
		Systolic Blood Pressure	-0.010584	0.0032095	0.0008
		Triglycerides	0.142576	0.0542078	0.0064

^a Wald p-value was shown instead of quasi-likelihood p-value due to unresolved convergence problems.

PM3006438222

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-3
Parameter Estimates for Biomarkers of Exposure with Half-Life Less Than or Equal to 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 8 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
Nicotine-N-glucuronide	nmol/mg Creatinine	Intercept	-0.568999	0.3332073	0.1073
		Self-exposure	0.027839	0.0093655	0.0051
		Alcohol Use	-0.339502	0.2153368	0.0898
		Job Status	-0.391376	0.1904927	0.0291
		Triglycerides	0.278758	0.1160564	0.0164
		Interaction between Self-exposure and Triglycerides	-0.005798	0.0027364	0.0775

PM3006438223

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-3
Parameter Estimates for Biomarkers of Exposure with Half-Life Less Than or Equal to 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 9 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
Cotinine-N-glucuronide	nmol/mg Creatinine	Intercept	0.081336	0.6032211	0.8863
		Self-exposure	0.055378	0.0099735	<0.0001
		Marital Status	-0.260415	0.1662658	0.1589
		Exposure to Cigarette Smoke in Places	0.198163	0.0548978	<0.0001
		Servings High in Fat	-0.000996	0.0054425	0.0737 ^a
		Systolic Blood Pressure	-0.011027	0.0047800	0.0109
		Triglycerides	0.266432	0.0923311	0.0040
		Exposure to Cigarette Smoke at the Work Place	0.126693	0.0482075	0.0003
		Interaction between Self-exposure and Exposure to Cigarette Smoke in Places	-0.011025	0.0027448	0.0005

^a Wald p-value was shown instead of quasi-likelihood p-value due to unresolved convergence problems.

PM3006438224

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-3
Parameter Estimates for Biomarkers of Exposure with Half-Life Less Than or Equal to 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 10 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
Carbon monoxide	ppm	Intercept	0.044879	0.4934992	0.9285
		Self-exposure	0.000611	0.0004393	0.1906
		Marital Status	0.210444	0.1355402	0.1442
		NAT2 Phenotyping	0.243929	0.1373252	0.0689
		Exposure to Cigarette Smoke From Visitors to Subject's Home	0.004389	0.0017123	0.0025
		Exposure to Cigarette Smoke From Spouse at Home	0.002377	0.0011702	0.0042
		Systolic Blood Pressure	-0.007730	0.0037335	0.0310
		Triglycerides	0.112438	0.0612380	0.0873
		Exposure to Cigarette Smoke in Vehicles	-0.048106	0.0258166	0.0656
		CYP1A2 Phenotyping	0.299765	0.1315416	0.0282 ^a

^a Wald p-value was shown instead of quasi-likelihood p-value due to unresolved convergence problems.

PM3006438225

Final Draft: 22 October 2003

Page 256 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-4
Parameter Estimates for Biomarkers of Exposure with Half-Life Greater Than 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 1 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
3-Aminobiphenyl-Hb adducts	pg/g hemoglobin	Intercept	0.878802	0.4792694	0.0541
		Self-exposure	0.000036	0.0000167	0.0320
		Marital Status	-0.409828	0.1316271	0.0015
		NAT2 Phenotyping	-0.475411	0.1246246	0.0002
		Exposure to Cigarette Smoke in Places	-0.002158	0.0007729	0.0090
		Exposure to Cigarette Smoke From Spouse at Home	0.000049	0.0000203	0.0090
		Systolic Blood Pressure	-0.013594	0.0036671	0.0001
		Triglycerides	0.147538	0.0554219	0.0051
		Use of Vitamins	0.226863	0.1314464	0.0824
		Exposure to Cigarette Smoke at the Work Place	0.000928	0.0004742	0.0310
		CYP1A2 Phenotyping	0.242086	0.1242907	0.0591 *

* Wald p-value was shown instead of quasi-likelihood p-value due to unresolved convergence problems.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-4
Parameter Estimates for Biomarkers of Exposure with Half-Life Greater Than 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 2 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
4-Aminobiphenyl-Hb adducts	pg/g hemoglobin	Intercept	0.816167	0.5099615	0.0910
		Self-exposure	0.000058	0.0000161	0.0002
		Marital Status	-0.339105	0.1420826	0.0157
		Exposure to Cigarette Smoke From Spouse at Home	0.000031	0.0000227	0.1273
		Systolic Blood Pressure	-0.011079	0.0037539	0.0016
		CYP1A2 Phenotyping	0.336045	0.1298167	0.0132 *

* Wald p-value was shown instead of quasi-likelihood p-value due to unresolved convergence problems.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-4
Parameter Estimates for Biomarkers of Exposure with Half-Life Greater Than 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 3 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
Sum of Nicotine and Nicotine metabolites	nmol/mg Creatinine	Intercept	0.434195	0.4079257	0.2471
		Self-exposure	0.000113	0.0000272	0.0001
		Body Mass Index	-0.038614	0.0123776	0.0008
		Use of Air Filtration Device	0.298491	0.1990008	0.1423 *
		Exposure to Chemicals and/or Engine Exhaust at the Job	0.821517	0.3306419	0.0073
		Job Status	-0.289569	0.1927031	0.1340
		NAT2 Phenotyping	0.396020	0.1922413	0.0291
		Exposure to Cigarette Smoke in Places	-0.004579	0.0014037	0.0016
		Servings High in Fat	-0.020295	0.0060751	0.0020 *
		Gender	-0.282066	0.1679733	0.0909
		Exposure to Cigarette Smoke From Spouse at Home	0.000105	0.0000323	0.0001
		Triglycerides	0.298730	0.0853020	0.0003

* Wald p-value was shown instead of quasi-likelihood p-value due to unresolved convergence problems.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-4
Parameter Estimates for Biomarkers of Exposure with Half-Life Greater Than 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 4 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
Nicotine	nmol/mg Creatinine	Intercept	-1.554667	0.2588453	<0.0001
		Self-exposure	0.000071	0.0000187	0.0002
		Age	0.016191	0.0059816	0.0090
		NAT2 Phenotyping	0.259864	0.1427175	0.0671
		Exposure to Cigarette Smoke in Places	-0.001426	0.0009147	0.1134
		Servings High in Fat	-0.005800	0.0048868	0.0993

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-4
Parameter Estimates for Biomarkers of Exposure with Half-Life Greater Than 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 5 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
Cotinine	nmol/mg Creatinine	Intercept	0.382162	0.5913577	0.5203
		Self-exposure	0.000072	0.0000191	0.0001
		Age	0.017243	0.0063941	0.0045
		Diastolic Blood Pressure	-0.023468	0.0081299	0.0025
		Use of Air Filtration Device	0.390216	0.1674217	0.0180
		Job Status	-0.255541	0.1587223	0.0999
		NAT2 Phenotyping	0.460028	0.1516883	0.0021
		Exposure to Cigarette Smoke in Places	-0.002411	0.0013117	0.0761
		Exposure to Cigarette Smoke From Spouse at Home	0.000047	0.0000253	0.0488
		Exposure to Cigarette Smoke in Vehicles	-0.002919	0.0009317	0.0097
		Use of Vitamins	0.298005	0.1553080	0.0515

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-4
Parameter Estimates for Biomarkers of Exposure with Half-Life Greater Than 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 6 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
NNAL plus NNAL-gluc	pmol/mg Creatinine	Intercept	-0.947362	0.1839637	<0.0001
		Self-exposure	0.000086	0.0000236	0.0001
		NAT2 Phenotyping	0.271581	0.1879421	0.1349
		Gender	-0.431957	0.1787089	0.0149
		Exposure to Cigarette Smoke From Spouse at Home	0.000041	0.0000291	0.1221
		Exposure to Cigarette Smoke in Vehicles	-0.002834	0.0010644	0.0189
		CYP1A2 Phenotyping	0.376097	0.1641859	0.0440

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-4
Parameter Estimates for Biomarkers of Exposure with Half-Life Greater Than 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 7 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
NNAL	pmol/mg Creatinine	Intercept	0.759077	0.6010235	0.2240
		Self-exposure	0.001076	0.0002300	<0.0001
		Age	0.019490	0.0071429	0.0049
		Diastolic Blood Pressure	-0.027017	0.0085610	0.0017
		Use of Air Filtration Device	0.483256	0.1742169	0.0001
		Marital Status	-0.373121	0.1551880	0.0144
		NAT2 Phenotyping	0.397988	0.1619116	0.0110
		Exposure to Cigarette Smoke in Places	-0.002619	0.0012911	0.0545
		Servings High in Fat	-0.008139	0.0044537	0.0029
		Gender	-0.383246	0.1452423	0.0062
		Exposure to Cigarette Smoke From Spouse at Home	0.000070	0.0000256	0.0037
		Exposure to Cigarette Smoke in Vehicles	-0.003323	0.0008725	0.0009

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-4
Parameter Estimates for Biomarkers of Exposure with Half-Life Greater Than 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 8 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
NNAL-O-glucuronide	pmol/mg Creatinine	Intercept	0.722334	0.6314869	0.2391
		Self-exposure	0.001888	0.0003438	0.0003
		Diastolic Blood Pressure	-0.031002	0.0097034	0.0008
		NAT2 Phenotyping	0.267340	0.1418965	0.0509
		Exposure to Cigarette Smoke From Visitors to Subject's Home	0.000337	0.0001483	0.0001
		Servings High in Fat	-0.012165	0.0049367	0.0039
		Exposure to Cigarette Smoke From Spouse at Home	0.000057	0.0000249	0.0143
		Triglycerides	0.323744	0.1118177	0.0011
		Exposure to Cigarette Smoke in Vehicles	-0.001941	0.0008989	0.0545
		Interaction between Self-exposure and Exposure to Cigarette Smoke From Visitors to Subject's Home	-0.000000	0.0000002	0.0005
		Interaction between Self-exposure and Triglycerides	-0.000263	0.0000907	0.0153

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-4
Parameter Estimates for Biomarkers of Exposure with Half-Life Greater Than 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 9 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
Nicotine-N-glucuronide	nmol/mg Creatinine	Intercept	0.690542	0.6243703	0.2538
		Self-exposure	-0.001717	0.0011198	0.1356
		Alcohol Use	-0.698390	0.2214538	0.0007
		Body Mass Index	-0.016946	0.0216194	0.4301
		Use of Air Filtration Device	0.362209	0.1852993	0.0074
		Job Status	-0.275891	0.1707846	0.0924
		Marital Status	-0.285040	0.1488958	0.0476
		NAT2 Phenotyping	0.357118	0.1608541	0.0231
		Exposure to Cigarette Smoke in Places	-0.004530	0.0016341	0.0017
		Exposure to Cigarette Smoke From Spouse at Home	0.000068	0.0000276	0.0054
		Exposure to Cigarette Smoke in Vehicles	-0.002157	0.0010182	0.0529
		CYP1A2 Phenotyping	-0.267544	0.1623573	0.1069
		Interaction between Self-exposure and Body Mass Index	0.000093	0.0000390	0.0212

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-4
Parameter Estimates for Biomarkers of Exposure with Half-Life Greater Than 3 Days
Exposure-Response Modeling Results From NLIN Procedure
(Page 10 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
Cotinine-N-glucuronide	nmol/mg Creatinine	Intercept	0.688627	0.7439985	0.3583
		Self-exposure	-0.001689	0.0011648	0.1708
		Alcohol Use	-0.404278	0.2301654	0.0708
		Body Mass Index	-0.052639	0.0260299	0.0459
		Marital Status	-0.347023	0.1626902	0.0334
		Exposure to Cigarette Smoke in Places	-0.004679	0.0009429	<0.0001
		Gender	-0.648378	0.1599572	<0.0001
		Exposure to Cigarette Smoke From Spouse at Home	0.000058	0.0000304	0.0404
		Triglycerides	0.361298	0.1162535	0.0018
		Exposure to Cigarette Smoke in Vehicles	0.004186	0.0028267	0.1486
		Exposure to Cigarette Smoke at the Work Place	0.003739	0.0014748	0.0011
		Interaction between Self-exposure and Body Mass Index	0.000142	0.0000459	0.0036
		Interaction between Self-exposure and Triglycerides	-0.000315	0.0001022	0.0248
		Interaction between Self-exposure and Exposure to Cigarette Smoke in vehicles	-0.000008	0.0000036	0.0451
		Interaction between Self-exposure and Exposure to Cigarette Smoke at the Work Place	-0.000005	0.0000021	0.0285

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-5
Variables Considered in Exposure-Response Modeling of Biomarkers of Effect

Variable	Source	Type	Definition
Age (years)*	Case Report Form	Continuous	Age at Enrollment
Body Mass Index (kg/m ²)*	Case Report Form	Continuous	Body Mass index at Screening
Gender	Case Report Form	Categorical	A Value of 1 for Males and 0 Otherwise
Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)	Labs	Continuous	Biomarker of Exposure

* Derived from data collected on the Case Report Form.

PM3006438236

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-6
Parameter Estimates for Biomarkers of Effect
Exposure-Response Modeling Results From NLIN Procedure
(Page 1 of 5)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
LDL-cholesterol	mg/dL	Intercept	-0.40983	0.386154	0.2991
		Age	0.01163	0.006103	0.0519
		Body Mass Index	0.00946	0.009116	0.3095
		Gender	0.07546	0.129099	0.5547
		Sum of Nicotine and Nicotine metabolites	0.00230	0.001594	0.1451

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-6
Parameter Estimates for Biomarkers of Effect
Exposure-Response Modeling Results From NLIN Procedure
(Page 2 of 5)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
Fibrinogen	mg/dL	Intercept	-0.11285	0.339175	0.7409
		Age	0.00705	0.005189	0.1707
		Body Mass Index	0.01537	0.008649	0.0814
		Gender	-0.30156	0.105195	0.0043
		Sum of Nicotine and Nicotine metabolites	0.00004	0.001341	0.9783

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-6
Parameter Estimates for Biomarkers of Effect
Exposure-Response Modeling Results From NLIN Procedure
(Page 3 of 5)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
C-reactive protein	mg/dL	Intercept	-1.91215	0.577965	0.0003
		Age	-0.00304	0.008105	0.6979
		Body Mass Index	0.04234	0.014609	0.0015
		Gender	-0.30327	0.179824	0.0883
		Sum of Nicotine and Nicotine metabolites	0.00288	0.002208	0.1738

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-6
Parameter Estimates for Biomarkers of Effect
Exposure-Response Modeling Results From NLIN Procedure
(Page 4 of 5)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
11-Dehydro-thromboxane B2	pg/mg Creatinine	Intercept	-1.19886	0.492844	0.0158
		Age	0.01026	0.007629	0.1896
		Body Mass Index	0.02720	0.012648	0.0262
		Gender	-0.12948	0.155677	0.4009
		Sum of Nicotine and Nicotine metabolites	0.00406	0.002017	0.0398

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-6
Parameter Estimates for Biomarkers of Effect
Exposure-Response Modeling Results From NLIN Procedure
(Page 5 of 5)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test
					P-value
8-Epi-prostaglandin F2 α	pg/mg Creatinine	Intercept	-0.55824	0.330361	0.0893
		Age	-0.00956	0.004861	0.0514
		Body Mass Index	0.01351	0.008097	0.0845
		Gender	-0.13548	0.106640	0.2018
		Sum of Nicotine and Nicotine metabolites	0.00698	0.001387	<0.0001

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

14.1.4 Supplementary Analysis

14.1.4.1 Laboratory Comparison

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.1-1
Analyses of Selected Biomarkers Measured by INBIFO and Covance Laboratories
(Page 1 of 11)

Biomarker	Unit	Week	Statistic	Difference ^a	P-value ^b
4-Aminobiphenyl-Hb adduct	pg/g hemoglobin	Week 1	N	15	0.1552
			MEAN	-6.12	
			SD, SE	15.484, 3.998	
			MEDIAN	-4.02	
			MIN, MAX	-48.13, 19.24	
			5%, 95%	-48.13, 19.24	
		Week 6	N	15	
			MEAN	-0.30	
			SD, SE	6.529, 1.686	
			MEDIAN	-0.94	
			MIN, MAX	-7.55, 20.89	
			5%, 95%	-7.55, 20.89	

^a Descriptive statistics for the difference between Covance value and INBIFO value. Difference calculated as Covance value - INBIFO value.

^b P-value derived from statistical analysis using Mixed procedure in SAS after controlling for week differences.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.1-1
Analyses of Selected Biomarkers Measured by INBIFO and Covance Laboratories
(Page 2 of 11)

Biomarker	Unit	Week	Statistic	Difference ^a	P-value ^b
Sum of Nicotine and Nicotine metabolites	nmol/mg Creatinine	Week 1	N	6	<0.0001
			MEAN	13.212	
			SD, SE	6.5616, 2.6788	
			MEDIAN	14.367	
			MIN, MAX	4.133, 21.126	
			5%, 95%	4.133, 21.126	
		Week 2	N	6	
			MEAN	14.421	
			SD, SE	9.7888, 3.9963	
			MEDIAN	12.960	
			MIN, MAX	5.578, 33.129	
			5%, 95%	5.578, 33.129	
		Week 3	N	5	
			MEAN	11.741	
			SD, SE	6.8063, 3.0439	
			MEDIAN	10.342	
			MIN, MAX	3.767, 20.156	
			5%, 95%	3.767, 20.156	

^a Descriptive statistics for the difference between Covance value and INBIFO value. Difference calculated as Covance value - INBIFO value.

^b P-value derived from statistical analysis using Mixed procedure in SAS after controlling for week differences.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.1-1
Analyses of Selected Biomarkers Measured by INBIFO and Covance Laboratories
(Page 3 of 11)

Biomarker	Unit	Week	Statistic	Difference ^a	P-value ^b
Nicotine	nmol/mg Creatinine	Week 1	N	6	<0.0001
			MEAN	0.794	
			SD, SE	0.5568, 0.2273	
			MEDIAN	0.765	
			MIN, MAX	0.188, 1.459	
			5%, 95%	0.188, 1.459	
		Week 2	N	6	
			MEAN	1.147	
			SD, SE	0.7302, 0.2981	
			MEDIAN	1.046	
			MIN, MAX	0.202, 2.347	
			5%, 95%	0.202, 2.347	
		Week 3	N	5	
			MEAN	0.563	
			SD, SE	0.2924, 0.1308	
			MEDIAN	0.655	
			MIN, MAX	0.193, 0.883	
			5%, 95%	0.193, 0.883	

^a Descriptive statistics for the difference between Covance value and INBIFO value. Difference calculated as Covance value - INBIFO value.

^b P-value derived from statistical analysis using Mixed procedure in SAS after controlling for week differences.

PM3006438245

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.1-1
Analyses of Selected Biomarkers Measured by INBIFO and Covance Laboratories
(Page 4 of 11)

Biomarker	Unit	Week	Statistic	Difference ^a	P-value ^b
Cotinine	nmol/mg Creatinine	Week 1	N	7	0.0002
			MEAN	0.742	
			SD, SE	0.7442, 0.2813	
			MEDIAN	0.509	
			MIN, MAX	-0.006, 1.842	
			5%, 95%	-0.006, 1.842	
		Week 2	N	6	
			MEAN	1.441	
			SD, SE	1.0953, 0.4471	
			MEDIAN	1.025	
			MIN, MAX	0.479, 3.178	
			5%, 95%	0.479, 3.178	
		Week 3	N	5	
			MEAN	0.782	
			SD, SE	0.7767, 0.3473	
			MEDIAN	0.946	
			MIN, MAX	-0.154, 1.758	
			5%, 95%	-0.154, 1.758	

^a Descriptive statistics for the difference between Covance value and INBIFO value. Difference calculated as Covance value - INBIFO value.

^b P-value derived from statistical analysis using Mixed procedure in SAS after controlling for week differences.

PM3006438246

Final Draft: 22 October 2003

Page 277 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.1-1
Analyses of Selected Biomarkers Measured by INBIFO and Covance Laboratories
(Page 5 of 11)

Biomarker	Unit	Week	Statistic	Difference ^a	P-value ^b
Trans-3-hydroxycotinine	nmol/mg Creatinine	Week 1	N	12	0.0015
			MEAN	1.599	
			SD, SE	2.2918, 0.6616	
			MEDIAN	0.368	
			MIN, MAX	0.001, 6.523	
			5%, 95%	0.001, 6.523	
		Week 2	N	11	
			MEAN	2.498	
			SD, SE	3.6010, 1.0857	
			MEDIAN	0.658	
			MIN, MAX	-0.005, 10.597	
			5%, 95%	-0.005, 10.597	
		Week 3	N	9	
			MEAN	1.526	
			SD, SE	3.5618, 1.1873	
			MEDIAN	0.176	
			MIN, MAX	0.000, 10.917	
			5%, 95%	0.000, 10.917	

^a Descriptive statistics for the difference between Covance value and INBIFO value. Difference calculated as Covance value - INBIFO value.

^b P-value derived from statistical analysis using Mixed procedure in SAS after controlling for week differences.

PM3006438247

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.1-1
Analyses of Selected Biomarkers Measured by INBIFO and Covance Laboratories
(Page 6 of 11)

Biomarker	Unit	Week	Statistic	Difference ^a	P-value ^b
Trans-3-hydroxycotinine-O-glucuronide	nmol/mg Creatinine	Week 1	N	8	<0.0001
			MEAN	2.935	
			SD, SE	2.5575, 0.9042	
			MEDIAN	2.542	
			MIN, MAX	-0.043, 6.480	
			5%, 95%	-0.043, 6.480	
		Week 2	N	7	
			MEAN	3.575	
			SD, SE	4.9873, 1.8850	
			MEDIAN	2.608	
			MIN, MAX	-1.196, 14.047	
			5%, 95%	-1.196, 14.047	
		Week 3	N	5	
			MEAN	3.691	
			SD, SE	1.1027, 0.4932	
			MEDIAN	3.509	
			MIN, MAX	2.197, 5.182	
			5%, 95%	2.197, 5.182	

^a Descriptive statistics for the difference between Covance value and INBIFO value. Difference calculated as Covance value - INBIFO value.

^b P-value derived from statistical analysis using Mixed procedure in SAS after controlling for week differences.

PM3006438248

Final Draft: 22 October 2003

Page 279 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.1-1
Analyses of Selected Biomarkers Measured by INBIFO and Covance Laboratories
(Page 7 of 11)

Biomarker	Unit	Week	Statistic	Difference ^a	P-value ^b
NNAL plus NNAL-gluc	pmol/mg Creatinine	Week 1	N	4	0.0079
			MEAN	0.768	
			SD, SE	0.5635, 0.2817	
			MEDIAN	0.801	
			MIN, MAX	0.126, 1.346	
			5%, 95%	0.126, 1.346	
		Week 3	N	5	
			MEAN	1.127	
			SD, SE	1.0251, 0.4585	
			MEDIAN	0.949	
			MIN, MAX	0.036, 2.498	
			5%, 95%	0.036, 2.498	

^a Descriptive statistics for the difference between Covance value and INBIFO value. Difference calculated as Covance value - INBIFO value.

^b P-value derived from statistical analysis using Mixed procedure in SAS after controlling for week differences.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.1-1
Analyses of Selected Biomarkers Measured by INBIFO and Covance Laboratories
(Page 8 of 11)

Biomarker	Unit	Week	Statistic	Difference ^a	P-value ^b
NNAL	pmol/mg Creatinine	Week 1	N	4	0.0009
			MEAN	0.244	
			SD, SE	0.1564, 0.0782	
			MEDIAN	0.184	
			MIN, MAX	0.137, 0.471	
			5%, 95%	0.137, 0.471	
		Week 3	N	4	
			MEAN	0.308	
			SD, SE	0.1405, 0.0703	
			MEDIAN	0.247	
			MIN, MAX	0.221, 0.518	
			5%, 95%	0.221, 0.518	

^a Descriptive statistics for the difference between Covance value and INBIFO value. Difference calculated as Covance value - INBIFO value.

^b P-value derived from statistical analysis using Mixed procedure in SAS after controlling for week differences.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.1-1
Analyses of Selected Biomarkers Measured by INBIFO and Covance Laboratories
(Page 9 of 11)

Biomarker	Unit	Week	Statistic	Difference ^a	P-value ^b
NNAL-O-glucuronide	pmol/mg Creatinine	Week 1	N	4	0.0126
			MEAN	0.524	
			SD, SE	0.5021, 0.2510	
			MEDIAN	0.606	
			MIN, MAX	-0.099, 0.983	
			5%, 95%	-0.099, 0.983	
		Week 3	N	4	
			MEAN	1.091	
			SD, SE	0.9310, 0.4655	
			MEDIAN	0.998	
			MIN, MAX	0.091, 2.276	
			5%, 95%	0.091, 2.276	

^a Descriptive statistics for the difference between Covance value and INBIFO value. Difference calculated as Covance value - INBIFO value.

^b P-value derived from statistical analysis using Mixed procedure in SAS after controlling for week differences.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438251

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.1-1
Analyses of Selected Biomarkers Measured by INBIFO and Covance Laboratories
(Page 10 of 11)

Biomarker	Unit	Week	Statistic	Difference ^a	P-value ^b
Nicotine-N-glucuronide	nmol/mg Creatinine	Week 1	N	6	0.5793
			MEAN	0.125	
			SD, SE	0.9589, 0.3915	
			MEDIAN	-0.133	
			MIN, MAX	-0.767, 1.940	
			5%, 95%	-0.767, 1.940	
		Week 2	N	6	
			MEAN	-0.183	
			SD, SE	1.2680, 0.5177	
			MEDIAN	-0.064	
			MIN, MAX	-2.316, 1.203	
			5%, 95%	-2.316, 1.203	
		Week 3	N	4	
			MEAN	0.678	
			SD, SE	1.1112, 0.5556	
			MEDIAN	0.961	
			MIN, MAX	-0.778, 1.567	
			5%, 95%	-0.778, 1.567	

^a Descriptive statistics for the difference between Covance value and INBIFO value. Difference calculated as Covance value - INBIFO value.

^b P-value derived from statistical analysis using Mixed procedure in SAS after controlling for week differences.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.1-1
Analyses of Selected Biomarkers Measured by INBIFO and Covance Laboratories
(Page 11 of 11)

Biomarker	Unit	Week	Statistic	Difference ^a	P-value ^b
Cotinine-N-glucuronide	nmol/mg Creatinine	Week 1	N	6	<0.0001
			MEAN	4.314	
			SD, SE	3.2818, 1.3398	
			MEDIAN	3.910	
			MIN, MAX	0.839, 10.239	
			5%, 95%	0.839, 10.239	
		Week 2	N	6	
			MEAN	3.269	
			SD, SE	1.7736, 0.7241	
			MEDIAN	3.625	
			MIN, MAX	0.418, 5.133	
			5%, 95%	0.418, 5.133	
		Week 3	N	5	
			MEAN	3.658	
			SD, SE	1.9952, 0.8923	
			MEDIAN	3.391	
			MIN, MAX	1.258, 6.685	
			5%, 95%	1.258, 6.685	

^a Descriptive statistics for the difference between Covance value and INBIFO value. Difference calculated as Covance value - INBIFO value.

^b P-value derived from statistical analysis using Mixed procedure in SAS after controlling for week differences.

PM3006438253

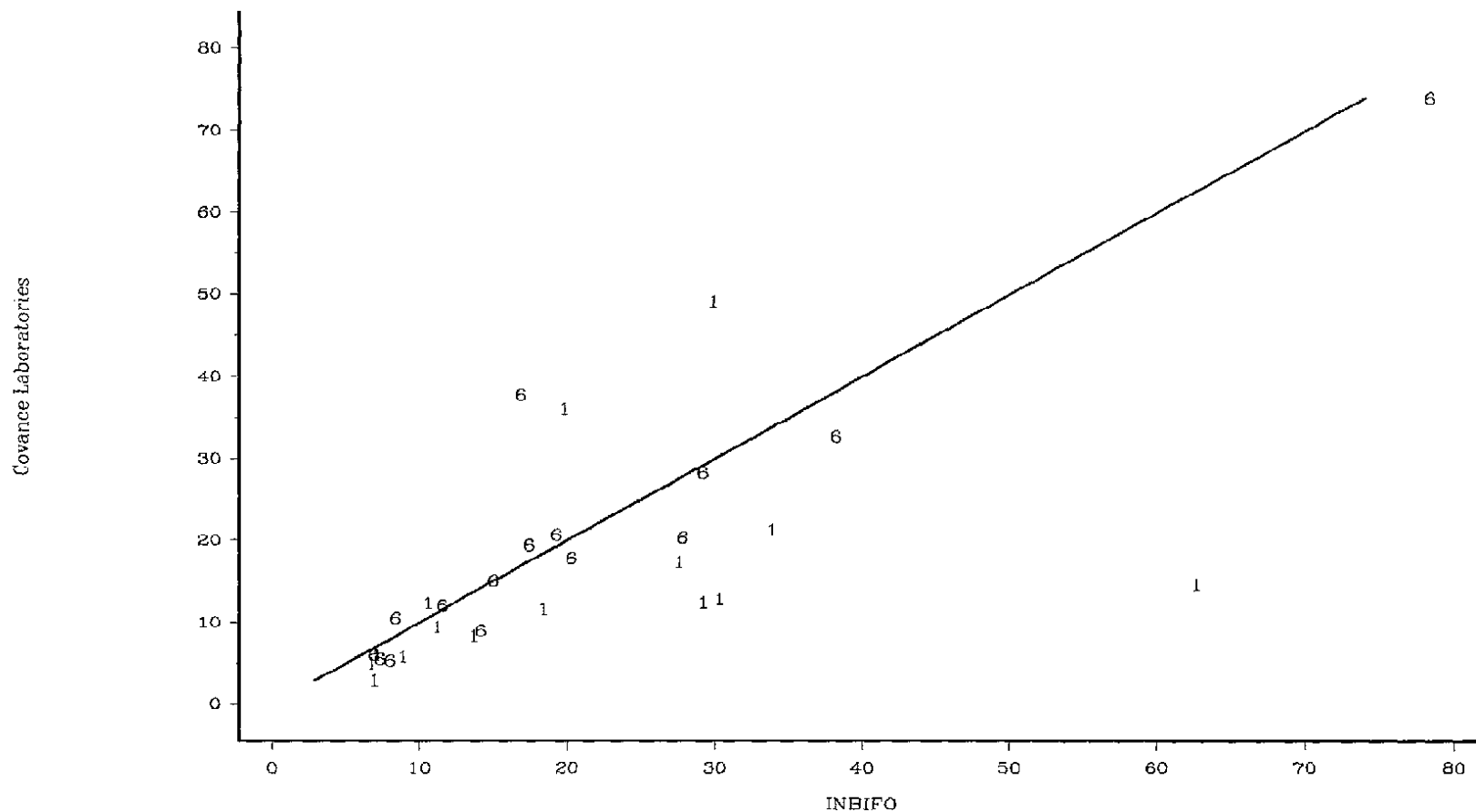
RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Plasma Blood Biomarker of Exposure:
4-Aminobiphenyl-Hb adduct (pg/g hemoglobin)

Diagonal line is $y=x$.
BLQ values were removed from this analysis.



1=Week 1; 6=Week 6

Figure 14.1.4.1-1
Covance by INBIFO for 4-Aminobiphenyl-Hb Adduct (pg/g hemoglobin)

Final Draft: 22 October 2003

Page 285 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

24-Hour Urine Biomarker of Exposure:
Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)

Diagonal line is $y=x$.
BLQ values were removed from this analysis.

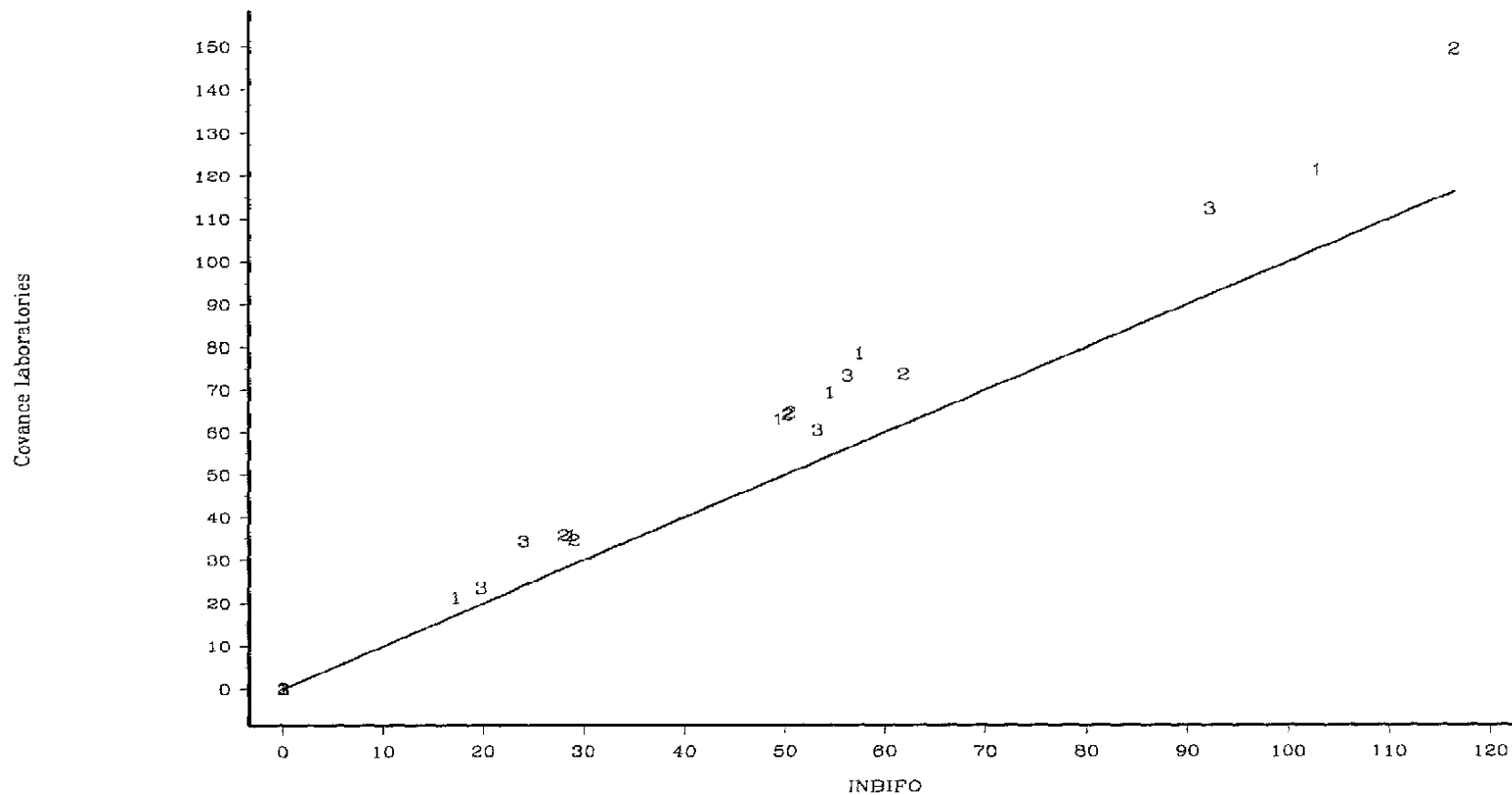


Figure 14.1.4.1-2
Covance by INBIFO for Sum of Nicotine and Nicotine Metabolites (nmol/mg Creatinine)

Final Draft: 22 October 2003

Page 286 of 15260

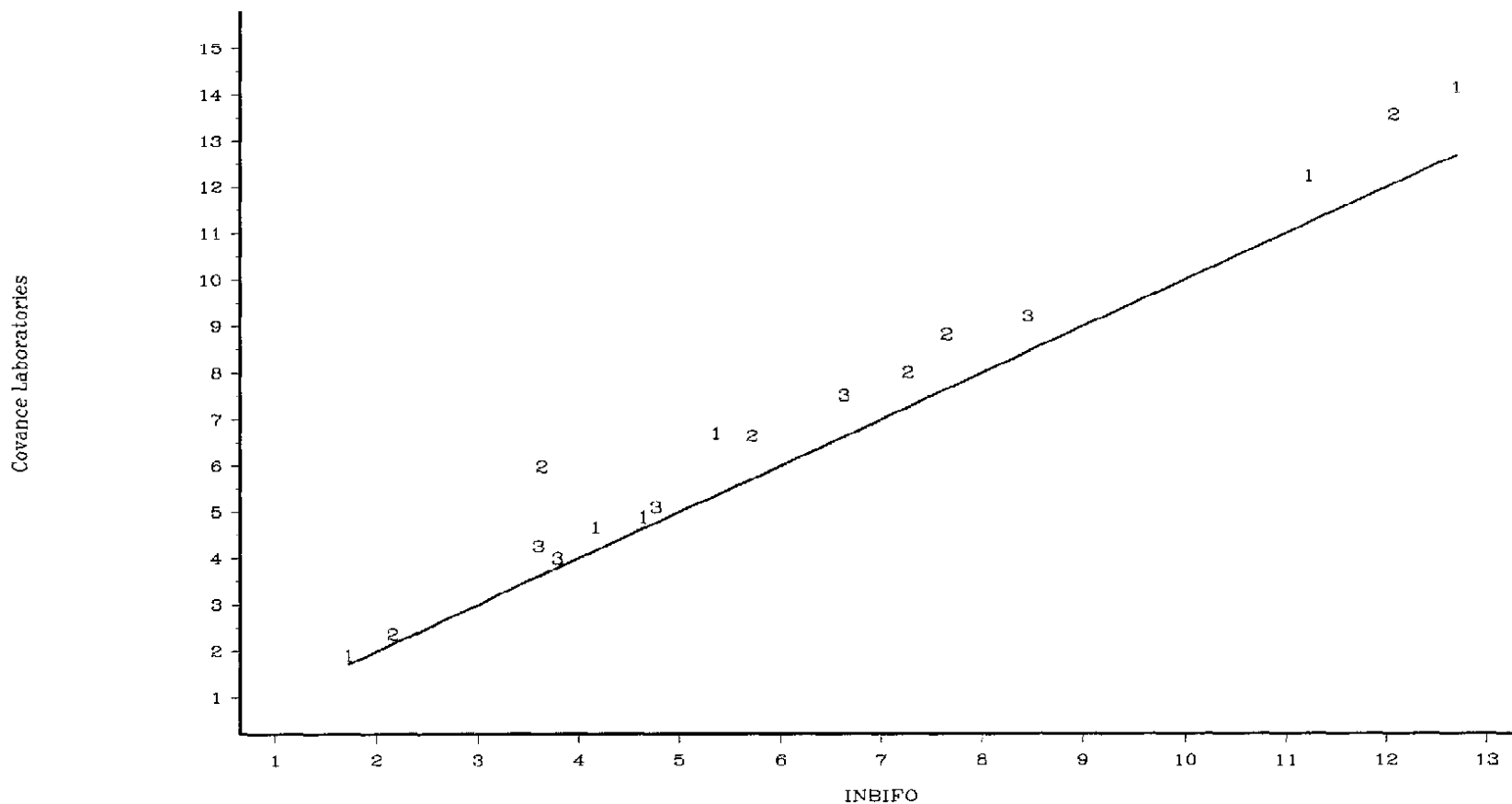
RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

24-Hour Urine Biomarker of Exposure:
Nicotine (nmol/mg Creatinine)

Diagonal line is $y=x$.
BLQ values were removed from this analysis.



1=Week 1; 2=Week 2; 3=Week 3

Figure 14.1.4.1-3
Covance by INBIFO for Nicotine (nmol/mg Creatinine)

Final Draft: 22 October 2003

Page 287 of 15260

PM3006438256

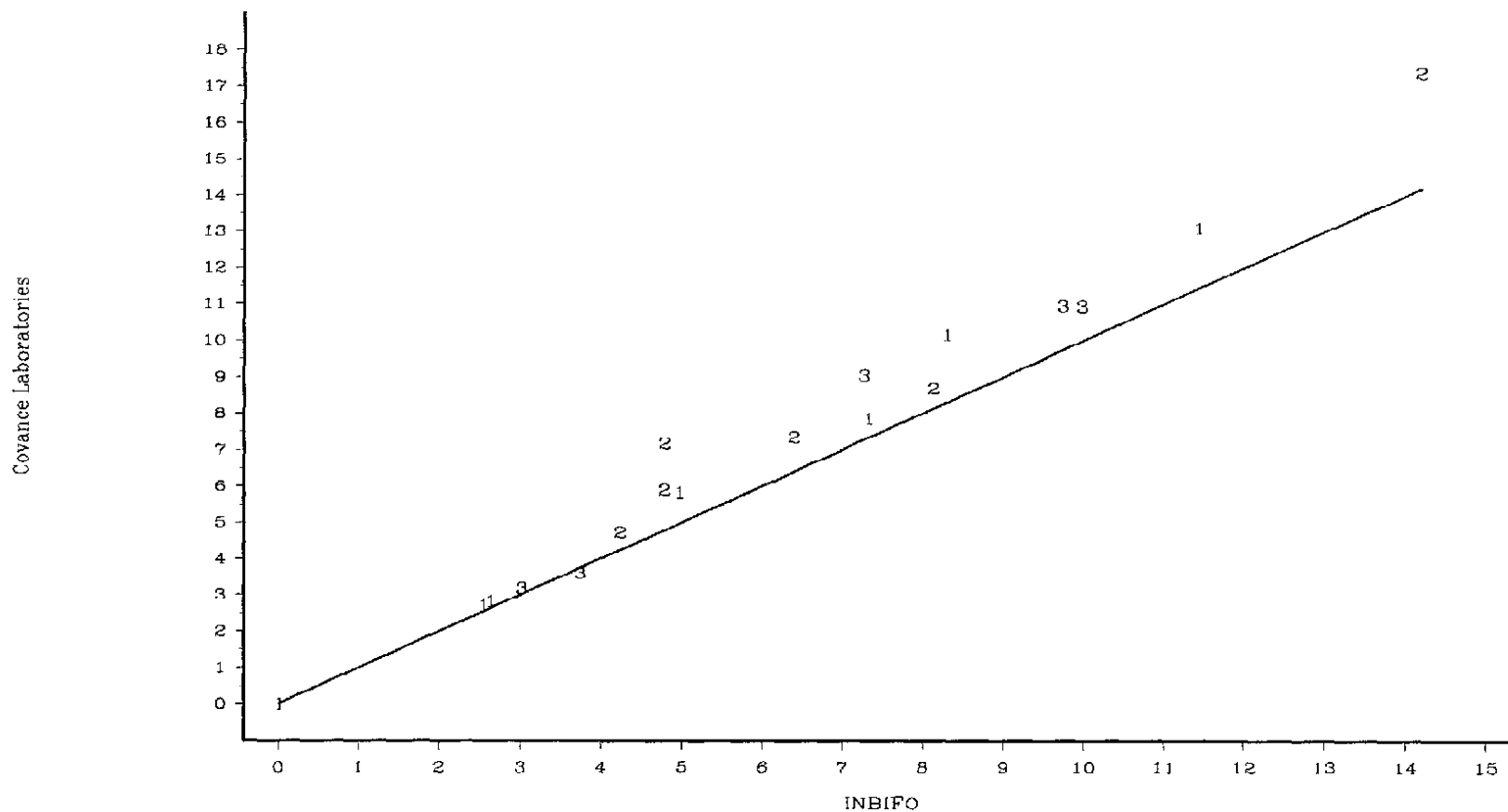
RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

24-Hour Urine Biomarker of Exposure:
Cotinine (nmol/mg Creatinine)

Diagonal line is $y=x$.
BLQ values were removed from this analysis.



1=Week 1; 2=Week 2; 3=Week 3

Figure 14.1.4.1-4
Covance by INBIFO for Cotinine (nmol/mg Creatinine)

Final Draft: 22 October 2003

Page 288 of 15260

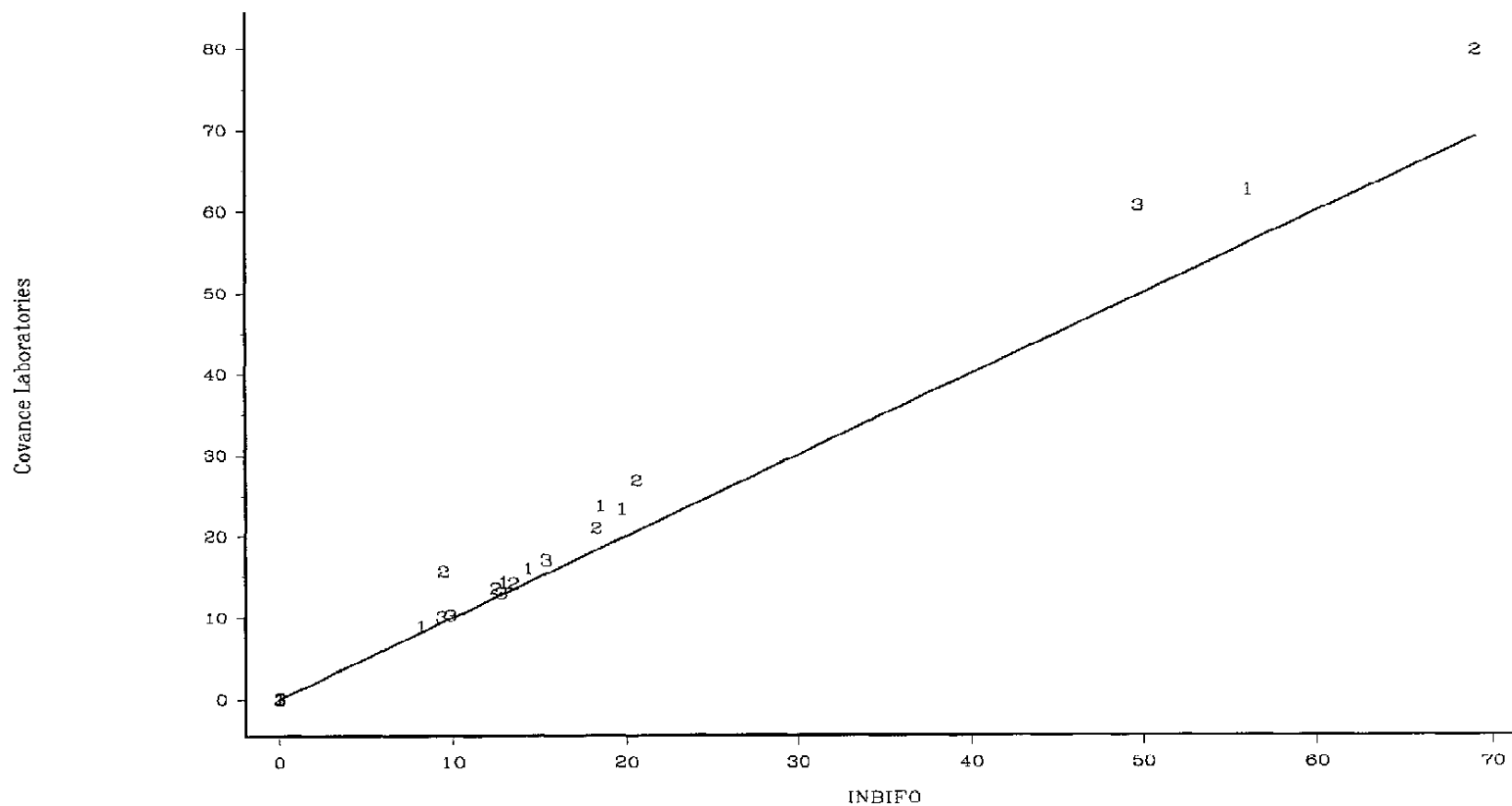
RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

24-Hour Urine Biomarker of Exposure:
Trans-3-hydroxycotinine (nmol/mg Creatinine)

Diagonal line is $y=x$.
BLQ values were removed from this analysis.



1=Week 1; 2=Week 2; 3=Week 3

Figure 14.1.4.1-5
Covance by INBIFO for Trans-3-hydroxycotinine (nmol/mg Creatinine)

Final Draft: 22 October 2003

Page 289 of 15260

PM3006438258

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

24 Hour Urine Biomarker of Exposure:
Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)

Diagonal line is $y=x$.
BLQ values were removed from this analysis.

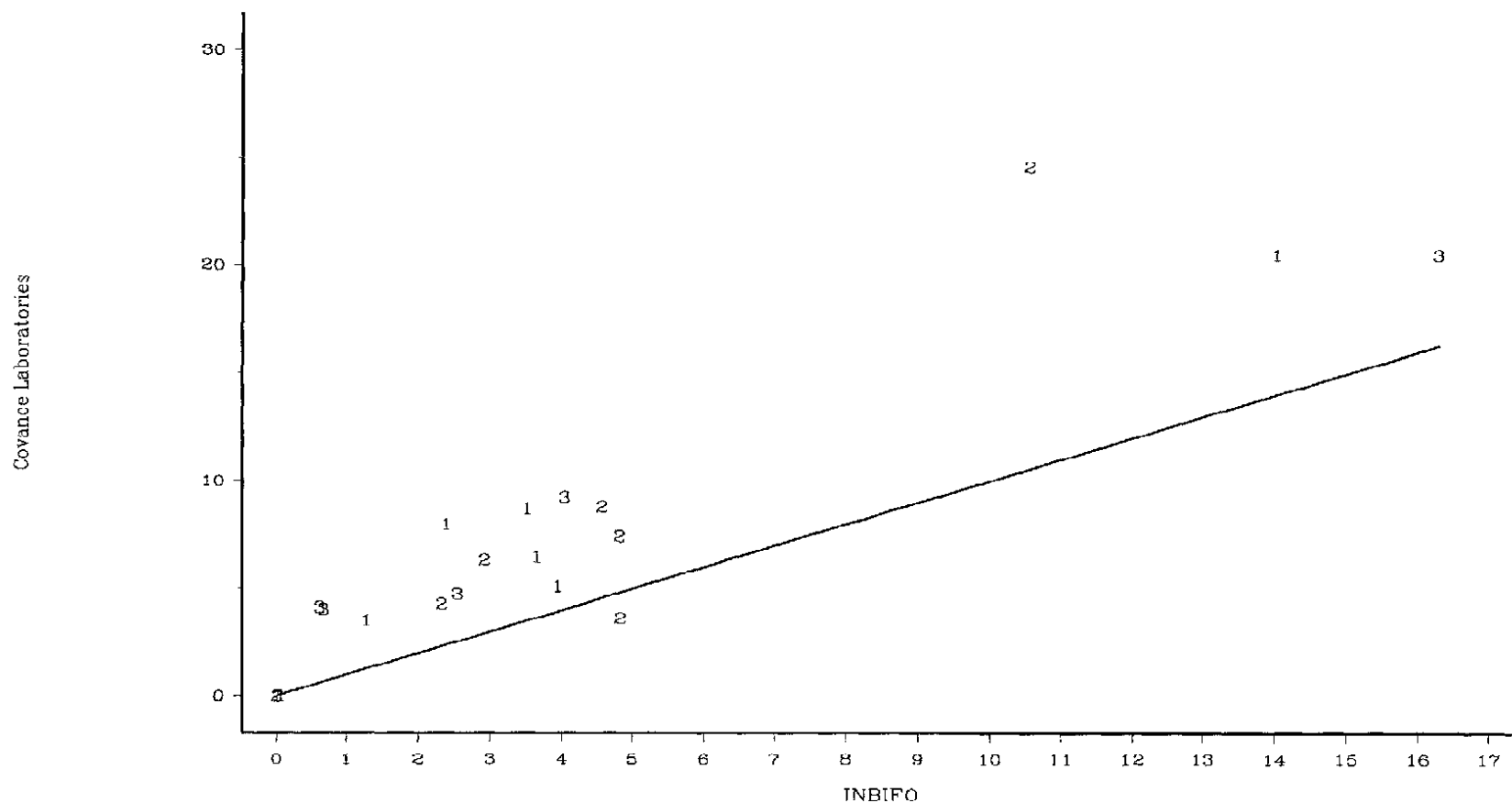


Figure 14.1.4.1-6
Covance by INBIFO for Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)

Final Draft: 22 October 2003

Page 290 of 15260

PM3006438259

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

24-Hour Urine Biomarker of Exposure:
NNAL plus NNAL-gluc (pmol/mg Creatinine)

Diagonal line is $y=x$.
BLQ values were removed from this analysis.

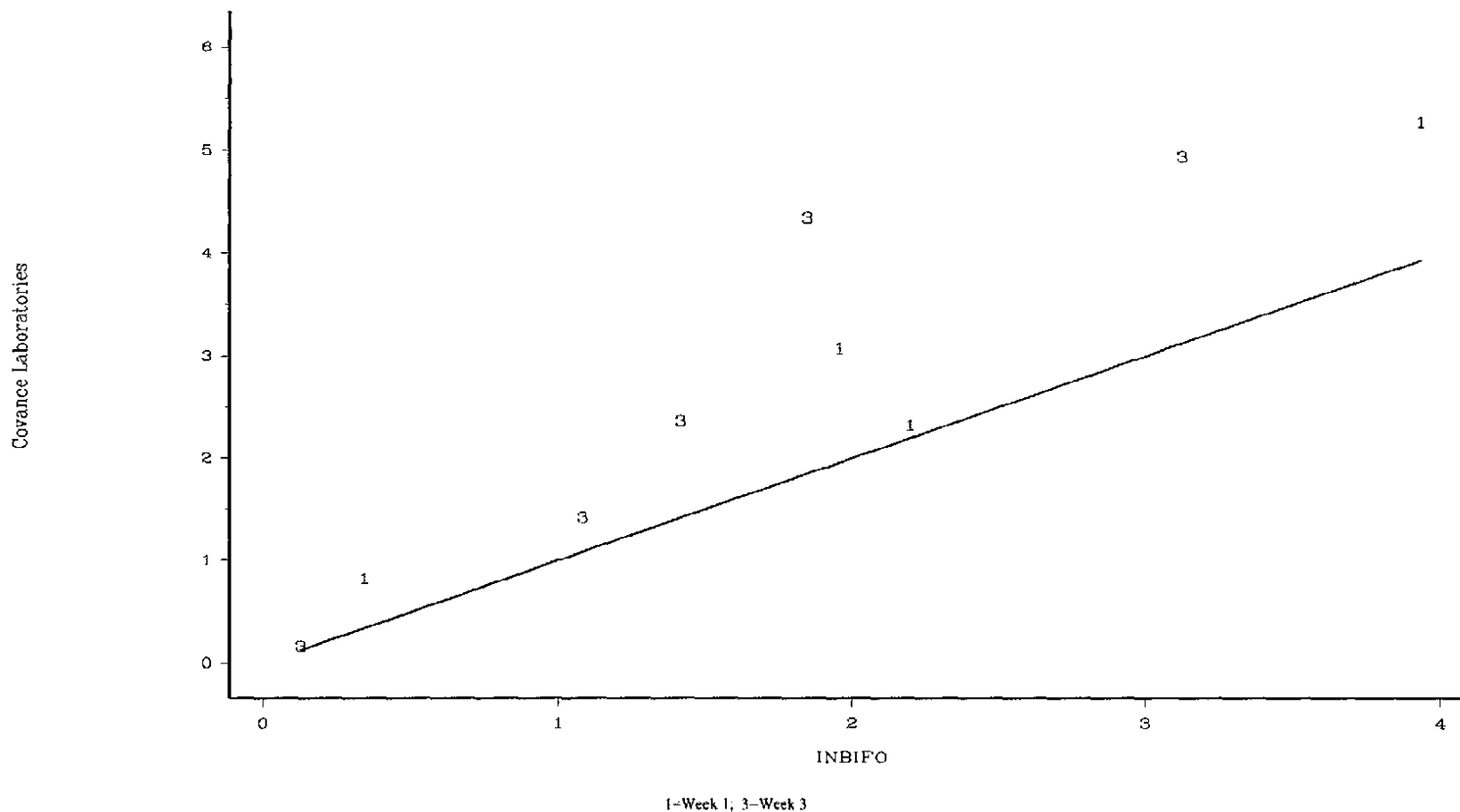


Figure 14.1.4.1-7
Covance by INBIFO for NNAL plus NNAL-gluc (pmol/mg Creatinine)

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

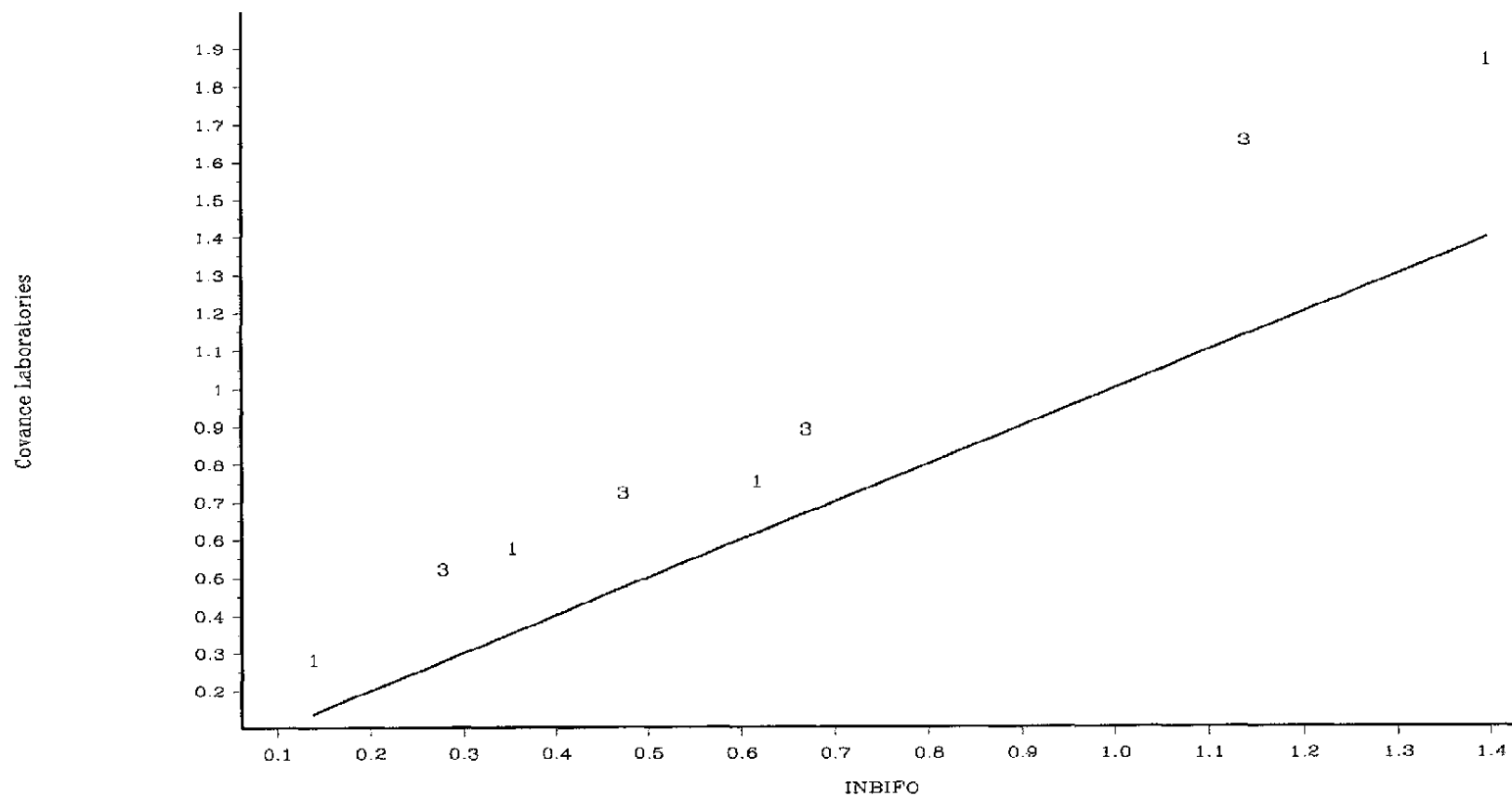
Final Draft: 22 October 2003

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

24-Hour Urine Biomarker of Exposure:
NNAL (pmol/mg Creatinine)
Diagonal line is $y=x$.
RLQ values were removed from this analysis.



1=Week 1; 3=Week 3

Figure 14.1.4.1-8
Covance by INBIFO for NNAL (pmol/mg Creatinine)

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

Final Draft: 22 October 2003

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

24-Hour Urine Biomarker of Exposure.
NNAL-O-glucuronide (pmol/mg Creatinine)

Diagonal line is $y=x$.
BLQ values were removed from this analysis.

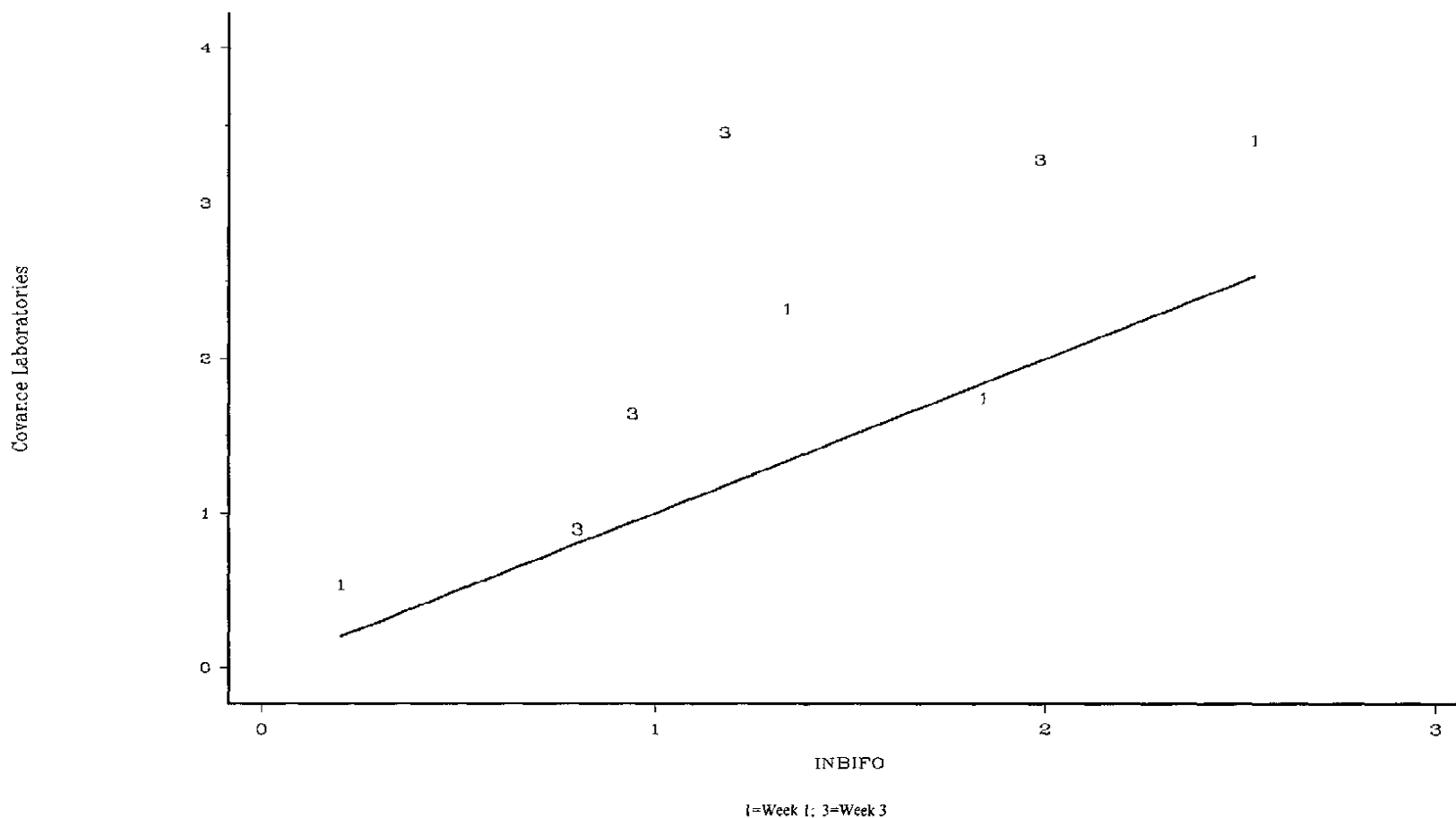


Figure 14.1.4.1-9
Covance by INBIFO for NNAL-O-glucuronide (pmol/mg Creatinine)

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

Final Draft: 22 October 2003

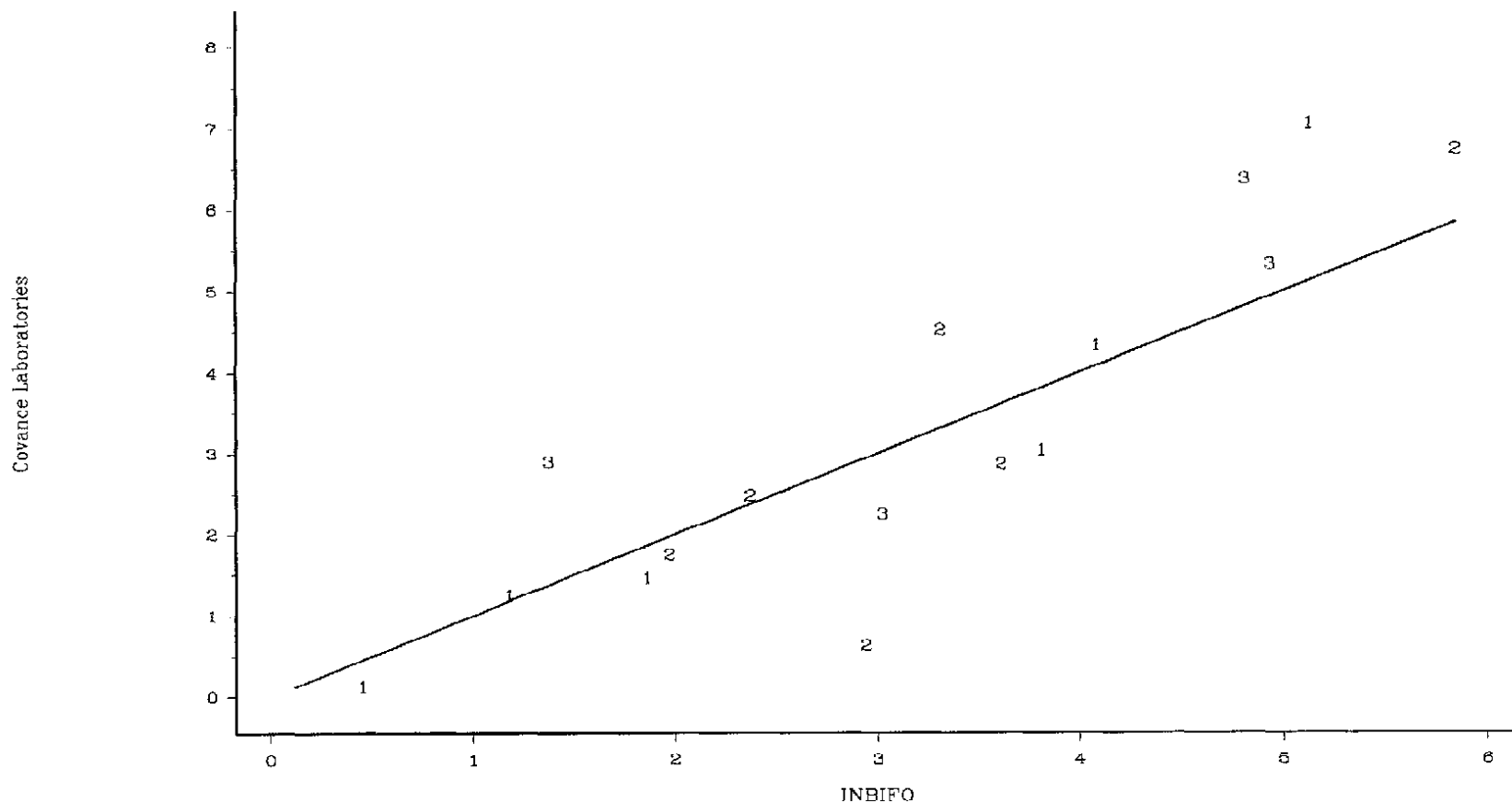
RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

24-Hour Urine Biomarker of Exposure:
Nicotine-N-glucuronide (nmol/mg Creatinine)

Diagonal line is $y=x$.
BLQ values were removed from this analysis.



1=Week 1; 2=Week 2; 3=Week 3

Figure 14.1.4.1-10
Covance by INBIFO for Nicotine-N-glucuronide (nmol/mg Creatinine)

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

24-Hour Urine Biomarker of Exposure:
Cotinine-N-glucuronide (nmol/mg Creatinine)

Diagonal line is $y=x$.
BLQ values were removed from this analysis.

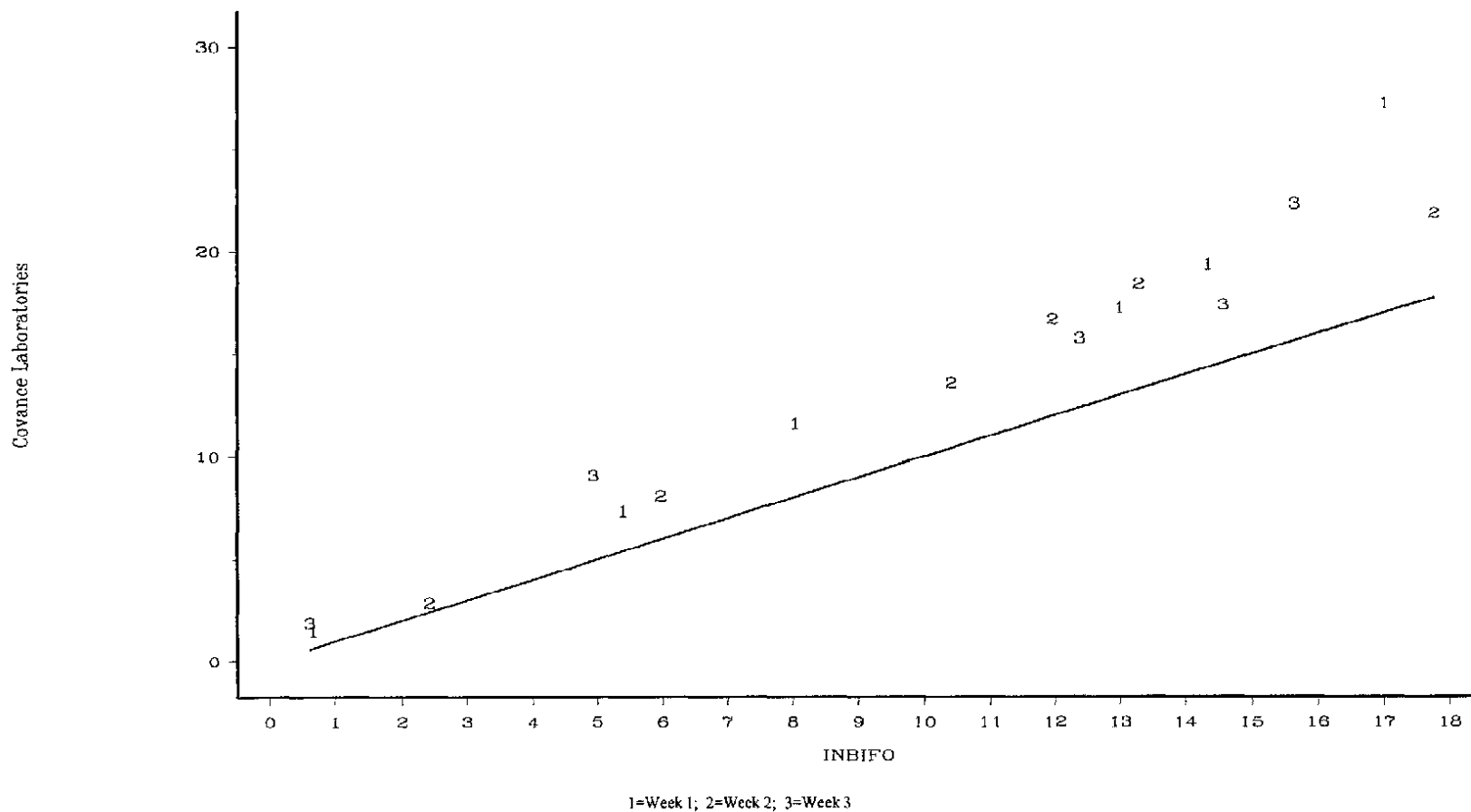


Figure 14.1.4.1-11
Covance by INBIFO for Cotinine-N-glucuronide (nmol/mg Creatinine)

PM3006438264

Final Draft: 22 October 2003

Page 295 of 15260

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 18 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 2	Harrogate Nicotine (nmol/mg Creatinine)	Other places	N	20	45	0.1713
			MEAN, GEO MEAN	0.104, NA	0.010, NA	
			SD, SE	0.3954, 0.0884	0.0063, 0.0009	
			MEDIAN	0.012	0.006	
		Away from home combined	MIN, MAX	0.000, 1.782	0.000, 0.025	0.0550
			5%, 95%	0.003, 0.934	0.000, 0.025	
			# of BLQ/ALQ Values	13/0	41/0	
		Spouse at home	N	23	42	0.0247
			MEAN, GEO MEAN	0.092, NA	0.010, NA	
			SD, SE	0.3687, 0.0769	0.0064, 0.0010	
			MEDIAN	0.012	0.006	
		Others at home	MIN, MAX	0.000, 1.782	0.000, 0.025	0.2778
			5%, 95%	0.006, 0.086	0.000, 0.025	
			# of BLQ/ALQ Values	14/0	40/0	
	Harrogate Cotinine (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0247
			MEAN, GEO MEAN	0.034, 0.033	0.016, NA	
			SD, SE	0.0085, 0.0060	0.0402, 0.0051	
			MEDIAN	0.034	0.011	
		Others at home	MIN, MAX	0.028, 0.040	0.000, 0.323	0.2778
			5%, 95%	0.028, 0.040	0.000, 0.028	
			# of BLQ/ALQ Values	0/0	47/0	
		Others at home	N	4	61	0.2778
			MEAN, GEO MEAN	0.019, 0.015	0.017, NA	
			SD, SE	0.0150, 0.0075	0.0408, 0.0052	
			MEDIAN	0.014	0.011	
		Others at home	MIN, MAX	0.006, 0.040	0.000, 0.323	0.2778
			5%, 95%	0.006, 0.040	0.000, 0.028	
			# of BLQ/ALQ Values	2/0	45/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-1
Statistical Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke Within 3-Day Period Before Sample Collection
(Page 1 of 7)

Timepoint	Analytical Lab Biomarker	Statistic	Exposed	Not-exposed	P-value*
Week 1	Harrogate 4-Aminobiphenyl-Hb adduct (pg/g hemoglobin)	N	30	35	0.0032
		MEAN, GEO MEAN	8.73, 7.91	6.04, 5.51	
		SD, SE	4.248, 0.776	2.668, 0.451	
		MEDIAN	7.56	5.50	
	Harrogate Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)	MIN, MAX	2.95, 23.25	2.49, 13.38	0.0040
		5%, 95%	3.94, 17.37	2.90, 11.63	
		# of BLQ/ALQ Values	0/0	0/0	
	Harrogate Nicotine (nmol/mg Creatinine)	N	30	35	0.4031
		MEAN, GEO MEAN	0.101, 0.053	0.048, NA	
		SD, SE	0.1522, 0.0278	0.0739, 0.0125	
		MEDIAN	0.044	0.033	
	Harrogate Cotinine (nmol/mg Creatinine)	MIN, MAX	0.005, 0.677	0.000, 0.340	0.4254
		5%, 95%	0.017, 0.447	0.016, 0.306	
		# of BLQ/ALQ Values	0/0	0/0	
	Harrogate Cotinine (nmol/mg Creatinine)	N	30	35	0.4254
		MEAN, GEO MEAN	0.028, NA	0.013, NA	
		SD, SE	0.0644, 0.0118	0.0174, 0.0029	
		MEDIAN	0.012	0.006	
	Harrogate Cotinine (nmol/mg Creatinine)	MIN, MAX	0.000, 0.271	0.000, 0.086	0.4254
		5%, 95%	0.000, 0.253	0.000, 0.074	
		# of BLQ/ALQ Values	19/0	32/0	
	Harrogate Cotinine (nmol/mg Creatinine)	N	30	35	0.4254
		MEAN, GEO MEAN	0.016, NA	0.011, NA	
		SD, SE	0.0220, 0.0040	0.0118, 0.0020	
		MEDIAN	0.011	0.006	
	Harrogate Cotinine (nmol/mg Creatinine)	MIN, MAX	0.000, 0.114	0.000, 0.057	0.4254
		5%, 95%	0.000, 0.057	0.000, 0.051	
		# of BLQ/ALQ Values	18/0	31/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

* P-value from Wilcoxon rank-sum test.

PM3006438266

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-1
Statistical Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke Within 3-Day Period Before Sample Collection
(Page 2 of 7)

Timepoint	Analytical Lab Biomarker	Statistic	Exposed	Not-exposed	P-value ^a
Week 1	Harrogate Trans-3-hydroxycotinine (nmol/mg Creatinine)	N	30	35	0.0073
		MEAN, GEO MEAN	0.035, 0.019	0.017, NA	
		SD, SE	0.0497, 0.0091	0.0320, 0.0054	
		MEDIAN	0.016	0.010	
		MIN, MAX	0.005, 0.219	0.000, 0.187	
		5%, 95%	0.005, 0.166	0.005, 0.068	
		# of BLQ/ALQ Values	8/0	14/0	
	Harrogate Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)	N	28	25	0.0284
		MEAN, GEO MEAN	0.009, NA	0.002, NA	
		SD, SE	0.0145, 0.0027	0.0044, 0.0009	
		MEDIAN	0.003	0.001	
		MIN, MAX	0.000, 0.053	0.000, 0.018	
		5%, 95%	0.000, 0.051	0.000, 0.012	
		# of BLQ/ALQ Values	8/0	14/0	
	Harrogate Nicotine-N-glucuronide (nmol/mg Creatinine)	N	29	33	0.0158
		MEAN, GEO MEAN	0.003, NA	0.001, NA	
		SD, SE	0.0047, 0.0009	0.0048, 0.0008	
		MEDIAN	0.000	0.000	
		MIN, MAX	0.000, 0.021	0.000, 0.023	
		5%, 95%	0.000, 0.012	0.000, 0.016	
		# of BLQ/ALQ Values	19/0	32/0	
	Harrogate Cotinine-N-glucuronide (nmol/mg Creatinine)	N	30	35	0.0012
		MEAN, GEO MEAN	0.012, NA	0.005, NA	
		SD, SE	0.0200, 0.0037	0.0143, 0.0024	
		MEDIAN	0.004	0.000	
		MIN, MAX	0.000, 0.075	0.000, 0.064	
		5%, 95%	0.000, 0.066	0.000, 0.055	
		# of BLQ/ALQ Values	18/0	31/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a P-value from Wilcoxon rank-sum test.

PM3006438267

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-1
Statistical Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke Within 3-Day Period Before Sample Collection
(Page 3 of 7)

Timepoint	Analytical Lab Biomarker	Statistic	Exposed	Not-exposed	P-value*
Week 2	Harrogate Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)	N	28	37	<.0001
		MEAN, GEO MEAN	0.212, 0.086	0.036, NA	
		SD, SE	0.5467, 0.1033	0.0345, 0.0057	
		MEDIAN	0.077	0.022	
		MIN, MAX	0.016, 2.938	0.000, 0.186	
		5%, 95%	0.017, 0.606	0.011, 0.105	
		# of BLQ/ALQ Values	0/0	0/0	
	Harrogate Nicotine (nmol/mg Creatinine)	N	28	37	0.0064
		MEAN, GEO MEAN	0.079, NA	0.009, NA	
		SD, SE	0.3342, 0.0632	0.0063, 0.0010	
		MEDIAN	0.012	0.006	
		MIN, MAX	0.000, 1.782	0.000, 0.025	
		5%, 95%	0.006, 0.086	0.000, 0.025	
		# of BLQ/ALQ Values	18/0	36/0	
	Harrogate Cotinine (nmol/mg Creatinine)	N	28	37	0.0008
		MEAN, GEO MEAN	0.027, NA	0.009, NA	
		SD, SE	0.0590, 0.0112	0.0071, 0.0012	
		MEDIAN	0.011	0.006	
		MIN, MAX	0.000, 0.323	0.000, 0.028	
		5%, 95%	0.006, 0.040	0.000, 0.028	
		# of BLQ/ALQ Values	12/0	35/0	
	Harrogate Trans-3-hydroxycotinine (nmol/mg Creatinine)	N	28	37	<.0001
		MEAN, GEO MEAN	0.059, 0.028	0.013, NA	
		SD, SE	0.0910, 0.0172	0.0117, 0.0019	
		MEDIAN	0.024	0.010	
		MIN, MAX	0.005, 0.411	0.000, 0.062	
		5%, 95%	0.005, 0.297	0.005, 0.036	
		# of BLQ/ALQ Values	6/0	11/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

* P-value from Wilcoxon rank-sum test.

PM3006438268

Final Draft: 22 October 2003

Page 299 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-1
Statistical Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke Within 3-Day Period Before Sample Collection
(Page 4 of 7)

Timepoint	Analytical Lab Biomarker	Statistic	Exposed	Not-exposed	P-value ^a
Week 2	Harrogate Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)	N	26	33	0.0061
		MEAN, GEO MEAN	0.017, NA	0.003, NA	
		SD, SE	0.0260, 0.0051	0.0051, 0.0009	
		MEDIAN	0.005	0.001	
		MIN, MAX	0.000, 0.105	0.000, 0.021	
		5%, 95%	0.000, 0.072	0.000, 0.016	
		# of BLQ/ALQ Values	6/0	11/0	
	Harrogate Nicotine-N-glucuronide (amol/mg Creatinine)	N	26	37	0.0001
		MEAN, GEO MEAN	0.013, NA	0.000, NA	
		SD, SE	0.0526, 0.0103	0.0013, 0.0002	
		MEDIAN	0.000	0.000	
		MIN, MAX	0.000, 0.270	0.000, 0.008	
		5%, 95%	0.000, 0.017	0.000, 0.000	
		# of BLQ/ALQ Values	18/0	36/0	
	Harrogate Cotinine-N-glucuronide (nmol/mg Creatinine)	N	28	37	<.0001
		MEAN, GEO MEAN	0.021, NA	0.003, NA	
		SD, SE	0.0371, 0.0070	0.0107, 0.0018	
		MEDIAN	0.012	0.000	
		MIN, MAX	0.000, 0.195	0.000, 0.058	
		5%, 95%	0.000, 0.045	0.000, 0.026	
		# of BLQ/ALQ Values	12/0	35/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a P value from Wilcoxon rank sum test.

PM3006438269

Final Draft: 22 October 2003

Page 300 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-1
Statistical Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke Within 3-Day Period Before Sample Collection
(Page 5 of 7)

Timepoint	Analytical Lab Biomarker	Statistic	Exposed	Not-exposed	P-value*
Week 3	Harrogate Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)	N	17	48	0.0057
		MEAN, GEO MEAN	0.104, 0.066	0.040, 0.032	
		SD, SE	0.1163, 0.0282	0.0404, 0.0058	
		MEDIAN	0.069	0.033	
		MIN, MAX	0.016, 0.470	0.011, 0.274	
		5%, 95%	0.016, 0.470	0.017, 0.085	
		# of BLQ/ALQ Values	0/0	0/0	
	Harrogate Nicotine (nmol/mg Creatinine)	N	17	48	0.9172
		MEAN, GEO MEAN	0.011, NA	0.010, NA	
		SD, SE	0.0110, 0.0027	0.0062, 0.0009	
		MEDIAN	0.012	0.006	
		MIN, MAX	0.000, 0.049	0.000, 0.031	
		5%, 95%	0.000, 0.049	0.006, 0.025	
		# of BLQ/ALQ Values	12/0	45/0	
	Harrogate Cotinine (nmol/mg Creatinine)	N	17	48	0.1767
		MEAN, GEO MEAN	0.017, NA	0.010, NA	
		SD, SE	0.0198, 0.0048	0.0079, 0.0011	
		MEDIAN	0.011	0.006	
		MIN, MAX	0.000, 0.079	0.000, 0.051	
		5%, 95%	0.000, 0.079	0.006, 0.023	
		# of BLQ/ALQ Values	7/0	43/0	
	Harrogate Trans-3-hydroxycotinine (nmol/mg Creatinine)	N	17	48	0.0031
		MEAN, GEO MEAN	0.043, 0.024	0.014, 0.010	
		SD, SE	0.0538, 0.0130	0.0153, 0.0022	
		MEDIAN	0.026	0.010	
		MIN, MAX	0.005, 0.213	0.005, 0.094	
		5%, 95%	0.005, 0.213	0.005, 0.042	
		# of BLQ/ALQ Values	0/0	30/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

* P-value from Wilcoxon rank-sum test.

PM3006438270

Final Draft: 22 October 2003

Page 301 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-1
Statistical Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke Within 3-Day Period Before Sample Collection
(Page 6 of 7)

Timepoint	Analytical Lab Biomarker	Statistic	Exposed	Not-exposed	P-value ^a
Week 3	Harrogate Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)	N	15	46	<.0001
		MEAN, GEO MEAN	0.013, NA	0.002, NA	
		SD, SE	0.0147, 0.0038	0.0063, 0.0009	
		MEDIAN	0.009	0.000	
		MIN, MAX	0.000, 0.050	0.000, 0.040	
		5%, 95%	0.000, 0.050	0.000, 0.008	
		# of BLQ/ALQ Values	0/0	30/0	
	Harrogate Nicotine-N-glucuronide (nmol/mg Creatinine)	N	17	48	0.0002
		MEAN, GEO MEAN	0.004, NA	0.000, NA	
		SD, SE	0.0055, 0.0013	0.0017, 0.0002	
		MEDIAN	0.002	0.000	
		MIN, MAX	0.000, 0.021	0.000, 0.008	
		5%, 95%	0.000, 0.021	0.000, 0.003	
		# of BLQ/ALQ Values	12/0	45/0	
	Harrogate Cotinine-N-glucuronide (nmol/mg Creatinine)	N	17	48	<.0001
		MEAN, GEO MEAN	0.017, NA	0.003, NA	
		SD, SE	0.0199, 0.0048	0.0097, 0.0014	
		MEDIAN	0.011	0.000	
		MIN, MAX	0.000, 0.067	0.000, 0.060	
		5%, 95%	0.000, 0.067	0.000, 0.015	
		# of BLQ/ALQ Values	7/0	43/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a P-value from Wilcoxon rank-sum test.

Final Draft: 22 October 2003

Page 302 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-1
Statistical Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke Within 3-Day Period Before Sample Collection
(Page 7 of 7)

Timepoint	Analytical Lab Biomarker	Statistic	Exposed	Not-exposed	P-value ^a
Week 6	Harrogate 4-Aminobiphenyl-Hb adduct (pg/g hemoglobin)	N	23	42	0.5974
		MEAN, GEO MEAN	9.45, 8.35	8.46, 7.75	
		SD, SE	5.727, 1.194	3.807, 0.587	
		MEDIAN	7.37	7.52	
		MIN, MAX	4.31, 27.86	4.09, 20.64	
		5%, 95%	4.49, 22.67	4.36, 15.32	
		# of BLQ/ALQ Values	0/0	0/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a P-value from Wilcoxon rank-sum test.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-2
Statistical Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke Within 3-Month Period Before Sample Collection at Enrollment
(Page 1 of 2)

Analytical Lab Biomarker	Statistic	Exposed	Not-exposed	P-value*
Harrogate 4-Aminobiphenyl-Hb adduct (pg/g hemoglobin)	N	28	37	0.0627
	MEAN, GEO MEAN	7.89, 7.25	6.82, 6.01	
	SD, SE	3.182, 0.601	4.050, 0.666	
	MEDIAN	7.56	6.22	
	MIN, MAX	2.95, 13.87	2.49, 23.25	
	5%, 95%	3.94, 13.59	2.90, 17.37	
	# of BLQ/ALQ Values	0/0	0/0	
Harrogate Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)	N	28	37	0.0021
	MEAN, GEO MEAN	0.126, 0.062	0.033, NA	
	SD, SE	0.1656, 0.0313	0.0266, 0.0044	
	MEDIAN	0.047	0.033	
	MIN, MAX	0.005, 0.677	0.000, 0.173	
	5%, 95%	0.016, 0.447	0.017, 0.051	
	# of BLQ/ALQ Values	0/0	0/0	
Harrogate Nicotine (nmol/mg Creatinine)	N	28	37	0.3843
	MEAN, GEO MEAN	0.034, NA	0.009, NA	
	SD, SE	0.0678, 0.0128	0.0044, 0.0007	
	MEDIAN	0.009	0.006	
	MIN, MAX	0.000, 0.271	0.000, 0.018	
	5%, 95%	0.000, 0.253	0.000, 0.018	
	# of BLQ/ALQ Values	16/0	35/0	
Harrogate Cotinine (nmol/mg Creatinine)	N	28	37	0.3676
	MEAN, GEO MEAN	0.019, NA	0.009, NA	
	SD, SE	0.0249, 0.0047	0.0051, 0.0008	
	MEDIAN	0.009	0.006	
	MIN, MAX	0.000, 0.114	0.000, 0.028	
	5%, 95%	0.000, 0.057	0.000, 0.017	
	# of BLQ/ALQ Values	15/0	34/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.
Week 1 biomarker data used.

* P-value from Wilcoxon rank-sum test.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-2
Statistical Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke Within 3-Month Period Before Sample Collection at Enrollment
(Page 2 of 2)

Analytical Lab Biomarker	Statistic	Exposed	Not-exposed	P-value ^a
Harrogate Trans-3-hydroxycotinine (nmol/mg Creatinine)	N	28	37	0.0004
	MEAN, GEO MEAN	0.045, 0.023	0.011, NA	
	SD, SE	0.0580, 0.0110	0.0075, 0.0012	
	MEDIAN	0.019	0.010	
	MIN, MAX	0.005, 0.219	0.000, 0.042	
	5%, 95%	0.005, 0.187	0.005, 0.026	
	# of BLQ/ALQ Values	4/0	18/0	
Harrogate Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)	N	25	28	<.0001
	MEAN, GEO MEAN	0.011, NA	0.002, NA	
	SD, SE	0.0147, 0.0029	0.0036, 0.0007	
	MEDIAN	0.006	0.000	
	MIN, MAX	0.000, 0.053	0.000, 0.015	
	5%, 95%	0.000, 0.051	0.000, 0.012	
	# of BLQ/ALQ Values	4/0	18/0	
Harrogate Nicotine-N-glucuronide (nmol/mg Creatinine)	N	26	36	0.0021
	MEAN, GEO MEAN	0.004, NA	0.001, NA	
	SD, SE	0.0063, 0.0012	0.0028, 0.0005	
	MEDIAN	0.000	0.000	
	MIN, MAX	0.000, 0.023	0.000, 0.016	
	5%, 95%	0.000, 0.021	0.000, 0.004	
	# of BLQ/ALQ Values	16/0	35/0	
Harrogate Cotinine-N-glucuronide (nmol/mg Creatinine)	N	28	37	<.0001
	MEAN, GEO MEAN	0.016, NA	0.002, NA	
	SD, SE	0.0223, 0.0042	0.0091, 0.0015	
	MEDIAN	0.008	0.000	
	MIN, MAX	0.000, 0.075	0.000, 0.055	
	5%, 95%	0.000, 0.066	0.000, 0.007	
	# of BLQ/ALQ Values	15/0	34/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

Week 1 biomarker data used.

^a P-value from Wilcoxon rank-sum test.

PM3006438274

Final Draft: 22 October 2003

Page 305 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 1 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 1	Harrogate 4-Aminobiphenyl-Hb adduct (pg/g hemoglobin)	Spouse at home	N	2	63	0.1656
			MEAN, GEO MEAN	9.17, 9.15	7.22, 6.44	
			SD, SE	0.856, 0.605	3.755, 0.473	
			MEDIAN	9.17	6.54	
			MIN, MAX	8.56, 9.77	2.49, 23.25	
			5%, 95%	8.56, 9.77	3.12, 13.59	
			# of BLQ/ALQ Values	0/0	0/0	
		Others at home	N	5	60	0.0518
			MEAN, GEO MEAN	9.81, 9.42	7.07, 6.32	
			SD, SE	3.126, 1.398	3.701, 0.478	
			MEDIAN	9.43	6.52	
			MIN, MAX	6.76, 13.87	2.49, 23.25	
			5%, 95%	6.76, 13.87	3.04, 13.49	
			# of BLQ/ALQ Values	0/0	0/0	
		At home combined	N	7	58	0.0141
			MEAN, GEO MEAN	9.63, 9.34	7.00, 6.24	
			SD, SE	2.595, 0.981	3.743, 0.491	
			MEDIAN	9.43	6.37	
			MIN, MAX	6.76, 13.87	2.49, 23.25	
			5%, 95%	6.76, 13.87	2.95, 13.59	
			# of BLQ/ALQ Values	0/0	0/0	
		Work	N	4	61	0.8165
			MEAN, GEO MEAN	8.04, 6.86	7.23, 6.49	
			SD, SE	4.788, 2.394	3.676, 0.471	
			MEDIAN	7.82	6.55	
			MIN, MAX	2.95, 13.59	2.49, 23.25	
			5%, 95%	2.95, 13.59	3.21, 13.38	
			# of BLQ/ALQ Values	0/0	0/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438275

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 2 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 1	Harrogate 4-Aminobiphenyl-Hb adduct (pg/g hemoglobin)	Vehicles	N	2	63	0.4141
			MEAN, GEO MEAN	5.42, 5.42	7.34, 6.55	
			SD, SE	0.071, 0.050	3.757, 0.473	
			MEDIAN	5.42	6.76	
			MIN, MAX	5.37, 5.47	2.49, 23.25	
			5%, 95%	5.37, 5.47	3.12, 13.59	
			# of BLQ/ALQ Values	0/0	0/0	
		Other places	N	21	44	0.0109
			MEAN, GEO MEAN	9.13, 8.27	6.39, 5.81	
			SD, SE	4.624, 1.009	2.843, 0.429	
			MEDIAN	7.59	6.22	
			MIN, MAX	3.94, 23.25	2.49, 13.87	
			5%, 95%	4.65, 17.37	2.95, 11.63	
			# of BLQ/ALQ Values	0/0	0/0	
		Away from home combined	N	25	40	0.0411
			MEAN, GEO MEAN	8.64, 7.74	6.43, 5.85	
			SD, SE	4.512, 0.902	2.859, 0.452	
			MEDIAN	7.53	6.38	
			MIN, MAX	2.95, 23.25	2.49, 13.87	
			5%, 95%	3.94, 17.37	3.01, 12.51	
			# of BLQ/ALQ Values	0/0	0/0	
	Harrogate Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0331
			MEAN, GEO MEAN	0.308, 0.275	0.065, NA	
			SD, SE	0.1966, 0.1390	0.1100, 0.0139	
			MEDIAN	0.308	0.033	
			MIN, MAX	0.169, 0.447	0.000, 0.677	
			5%, 95%	0.169, 0.447	0.017, 0.306	
			# of BLQ/ALQ Values	0/0	0/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438276

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 3 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 1	Harrogate Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)	Others at home	N	5	60	0.2960
			MEAN, GEO MEAN	0.180, 0.074	0.064, NA	
			SD, SE	0.2812, 0.1257	0.0944, 0.0122	
			MEDIAN	0.045	0.033	
			MIN, MAX	0.017, 0.677	0.000, 0.447	
			5%, 95%	0.017, 0.677	0.017, 0.323	
			# of BLQ/ALQ Values	0/0	0/0	
		At home combined	N	7	58	0.0361
			MEAN, GEO MEAN	0.216, 0.107	0.056, NA	
			SD, SE	0.2511, 0.0949	0.0799, 0.0105	
			MEDIAN	0.127	0.033	
			MIN, MAX	0.017, 0.677	0.000, 0.430	
			5%, 95%	0.017, 0.677	0.016, 0.306	
			# of BLQ/ALQ Values	0/0	0/0	
		Work	N	4	61	0.0774
			MEAN, GEO MEAN	0.082, 0.073	0.072, NA	
			SD, SE	0.0428, 0.0214	0.1223, 0.0157	
			MEDIAN	0.080	0.033	
			MIN, MAX	0.033, 0.136	0.000, 0.677	
			5%, 95%	0.033, 0.136	0.017, 0.340	
			# of BLQ/ALQ Values	0/0	0/0	
		Vehicles	N	2	63	0.1446
			MEAN, GEO MEAN	0.061, 0.060	0.073, NA	
			SD, SE	0.0141, 0.0100	0.1207, 0.0152	
			MEDIAN	0.061	0.033	
			MIN, MAX	0.051, 0.071	0.000, 0.677	
			5%, 95%	0.051, 0.071	0.017, 0.340	
			# of BLQ/ALQ Values	0/0	0/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438277

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 4 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 1	Harrogate Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)	Other places	N	21	44	0.1091
			MEAN, GEO MEAN	0.097, 0.048	0.061, NA	
			SD, SE	0.1618, 0.0353	0.0917, 0.0138	
			MEDIAN	0.043	0.033	
			MIN, MAX	0.005, 0.677	0.000, 0.447	
			5%, 95%	0.017, 0.430	0.017, 0.306	
			# of BLQ/ALQ Values	0/0	0/0	
		Away from home combined	N	25	40	0.0184
			MEAN, GEO MEAN	0.093, 0.050	0.060, NA	
			SD, SE	0.1488, 0.0298	0.0954, 0.0151	
			MEDIAN	0.043	0.033	
			MIN, MAX	0.005, 0.677	0.000, 0.447	
			5%, 95%	0.017, 0.430	0.017, 0.323	
			# of BLQ/ALQ Values	0/0	0/0	
	Harrogate Nicotine (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0271
			MEAN, GEO MEAN	0.043, 0.041	0.019, NA	
			SD, SE	0.0170, 0.0120	0.0463, 0.0058	
			MEDIAN	0.043	0.006	
			MIN, MAX	0.031, 0.055	0.000, 0.271	
			5%, 95%	0.031, 0.055	0.000, 0.074	
			# of BLQ/ALQ Values	0/0	51/0	
		Others at home	N	5	60	0.5195
			MEAN, GEO MEAN	0.058, 0.017	0.017, NA	
			SD, SE	0.1092, 0.0488	0.0366, 0.0047	
			MEDIAN	0.012	0.006	
			MIN, MAX	0.006, 0.253	0.000, 0.271	
			5%, 95%	0.006, 0.253	0.000, 0.065	
			# of BLQ/ALQ Values	3/0	48/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438278

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 5 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 1	Harrogate Nicotine (nmol/mg Creatinine)	At home combined	N	7	58	0.0724
			MEAN, GEO MEAN	0.054, 0.022	0.016, NA	
			SD, SE	0.0897, 0.0339	0.0368, 0.0048	
			MEDIAN	0.012	0.006	
			MIN, MAX	0.006, 0.253	0.000, 0.271	
			5%, 95%	0.006, 0.253	0.000, 0.074	
			# of BLQ/ALQ Values	3/0	48/0	
		Work	N	4	61	0.8497
			MEAN, GEO MEAN	0.011, 0.009	0.020, NA	
			SD, SE	0.0057, 0.0029	0.0473, 0.0061	
			MEDIAN	0.009	0.006	
			MIN, MAX	0.006, 0.018	0.000, 0.271	
			5%, 95%	0.006, 0.018	0.000, 0.074	
			# of BLQ/ALQ Values	1/0	50/0	
		Vehicles	N	2	63	0.7000
			MEAN, GEO MEAN	0.012, 0.010	0.020, NA	
			SD, SE	0.0085, 0.0060	0.0466, 0.0059	
			MEDIAN	0.012	0.006	
			MIN, MAX	0.006, 0.018	0.000, 0.271	
			5%, 95%	0.006, 0.018	0.000, 0.074	
			# of BLQ/ALQ Values	1/0	50/0	
		Other places	N	21	44	0.8281
			MEAN, GEO MEAN	0.033, NA	0.014, NA	
			SD, SE	0.0764, 0.0167	0.0171, 0.0026	
			MEDIAN	0.012	0.006	
			MIN, MAX	0.000, 0.271	0.000, 0.086	
			5%, 95%	0.000, 0.253	0.006, 0.055	
			# of BLQ/ALQ Values	14/0	37/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438279

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 6 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 1	Harrogate Nicotine (nmol/mg Creatinine)	Away from home combined	N	25	40	0.7569
			MEAN, GEO MEAN	0.029, NA	0.014, NA	
			SD, SE	0.0702, 0.0140	0.0179, 0.0028	
			MEDIAN	0.012	0.006	
			MIN, MAX	0.000, 0.271	0.000, 0.086	
			5%, 95%	0.000, 0.253	0.003, 0.065	
			# of BLQ/ALQ Values	16/0	35/0	
	Harrogate Cotinine (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0308
			MEAN, GEO MEAN	0.034, 0.032	0.013, NA	
			SD, SE	0.0156, 0.0110	0.0170, 0.0021	
			MEDIAN	0.034	0.006	
			MIN, MAX	0.023, 0.045	0.000, 0.114	
			5%, 95%	0.023, 0.045	0.000, 0.051	
			# of BLQ/ALQ Values	0/0	49/0	
		Others at home	N	5	60	0.5387
			MEAN, GEO MEAN	0.030, 0.014	0.012, NA	
			SD, SE	0.0472, 0.0211	0.0122, 0.0016	
			MEDIAN	0.011	0.006	
			MIN, MAX	0.006, 0.114	0.000, 0.057	
			5%, 95%	0.006, 0.114	0.000, 0.048	
			# of BLQ/ALQ Values	3/0	46/0	
		At home combined	N	7	58	0.0813
			MEAN, GEO MEAN	0.031, 0.018	0.011, NA	
			SD, SE	0.0392, 0.0148	0.0115, 0.0015	
			MEDIAN	0.011	0.006	
			MIN, MAX	0.006, 0.114	0.000, 0.057	
			5%, 95%	0.006, 0.114	0.000, 0.051	
			# of BLQ/ALQ Values	3/0	46/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438280

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 7 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 1	Harrogate Cotinine (nmol/mg Creatinine)	Work	N	4	61	0.9076
			MEAN, GEO MEAN	0.010, 0.009	0.013, NA	
			SD, SE	0.0052, 0.0026	0.0178, 0.0023	
			MEDIAN	0.009	0.006	
			MIN, MAX	0.006, 0.017	0.000, 0.114	
			5%, 95%	0.006, 0.017	0.000, 0.051	
			# of BLQ/ALQ Values	1/0	48/0	
		Vehicles	N	2	63	0.7467
			MEAN, GEO MEAN	0.012, 0.010	0.013, NA	
			SD, SE	0.0078, 0.0055	0.0175, 0.0022	
			MEDIAN	0.012	0.006	
			MIN, MAX	0.006, 0.017	0.000, 0.114	
			5%, 95%	0.006, 0.017	0.000, 0.051	
			# of BLQ/ALQ Values	1/0	48/0	
		Other places	N	21	44	0.7770
			MEAN, GEO MEAN	0.015, NA	0.012, NA	
			SD, SE	0.0253, 0.0055	0.0119, 0.0018	
			MEDIAN	0.006	0.009	
			MIN, MAX	0.000, 0.114	0.000, 0.057	
			5%, 95%	0.000, 0.057	0.006, 0.045	
			# of BLQ/ALQ Values	13/0	36/0	
		Away from home combined	N	25	40	0.7635
			MEAN, GEO MEAN	0.015, NA	0.012, NA	
			SD, SE	0.0232, 0.0046	0.0125, 0.0020	
			MEDIAN	0.011	0.006	
			MIN, MAX	0.000, 0.114	0.000, 0.057	
			5%, 95%	0.000, 0.057	0.003, 0.048	
			# of BLQ/ALQ Values	15/0	34/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438281

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2.3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 8 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 1	Harrogate Trans-3-hydroxycotinine (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0228
			MEAN, GEO MEAN	0.149, 0.131	0.022, NA	
			SD, SE	0.0997, 0.0705	0.0338, 0.0043	
			MEDIAN	0.149	0.010	
			MIN, MAX	0.078, 0.219	0.000, 0.187	
			5%, 95%	0.078, 0.219	0.005, 0.083	
			# of BLQ/ALQ Values	0/0	22/0	
		Others at home	N	5	60	0.3772
			MEAN, GEO MEAN	0.048, 0.022	0.024, NA	
			SD, SE	0.0676, 0.0302	0.0393, 0.0051	
			MEDIAN	0.016	0.010	
			MIN, MAX	0.005, 0.166	0.000, 0.219	
			5%, 95%	0.005, 0.166	0.005, 0.091	
			# of BLQ/ALQ Values	1/0	21/0	
		At home combined	N	7	58	0.0415
			MEAN, GEO MEAN	0.077, 0.037	0.019, NA	
			SD, SE	0.0844, 0.0319	0.0293, 0.0038	
			MEDIAN	0.042	0.010	
			MIN, MAX	0.005, 0.219	0.000, 0.187	
			5%, 95%	0.005, 0.219	0.005, 0.083	
			# of BLQ/ALQ Values	1/0	21/0	
		Work	N	4	61	0.0828
			MEAN, GEO MEAN	0.032, 0.027	0.025, NA	
			SD, SE	0.0218, 0.0109	0.0429, 0.0055	
			MEDIAN	0.029	0.010	
			MIN, MAX	0.010, 0.062	0.000, 0.219	
			5%, 95%	0.010, 0.062	0.005, 0.099	
			# of BLQ/ALQ Values	1/0	21/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438282

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 9 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 1	Harrogate Trans-3-hydroxycotinine (nmol/mg Creatinine)	Vehicles	N	2	63	0.2201
			MEAN, GEO MEAN	0.024, 0.022	0.026, NA	
			SD, SE	0.0106, 0.0075	0.0425, 0.0053	
			MEDIAN	0.024	0.010	
			MIN, MAX	0.016, 0.031	0.000, 0.219	
			5%, 95%	0.016, 0.031	0.005, 0.099	
			# of BLQ/ALQ Values	1/0	21/0	
		Other places	N	21	44	0.1276
			MEAN, GEO MEAN	0.029, 0.017	0.024, NA	
			SD, SE	0.0398, 0.0087	0.0431, 0.0065	
			MEDIAN	0.016	0.010	
			MIN, MAX	0.005, 0.166	0.000, 0.219	
			5%, 95%	0.005, 0.099	0.005, 0.078	
			# of BLQ/ALQ Values	5/0	17/0	
		Away from home combined	N	25	40	0.0290
			MEAN, GEO MEAN	0.029, 0.018	0.023, NA	
			SD, SE	0.0373, 0.0075	0.0447, 0.0071	
			MEDIAN	0.016	0.010	
			MIN, MAX	0.005, 0.166	0.000, 0.219	
			5%, 95%	0.005, 0.099	0.005, 0.133	
			# of BLQ/ALQ Values	7/0	15/0	
	Harrogate Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)	Spouse at home	N	2	51	0.0198
			MEAN, GEO MEAN	0.039, 0.036	0.005, NA	
			SD, SE	0.0198, 0.0140	0.0090, 0.0013	
			MEDIAN	0.039	0.001	
			MIN, MAX	0.025, 0.053	0.000, 0.051	
			5%, 95%	0.025, 0.053	0.000, 0.018	
			# of BLQ/ALQ Values	0/0	22/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438283

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 10 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 1	Harrogate Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)	Others at home	N	5	48	0.2798
			MEAN, GEO MEAN	0.013, NA	0.005, NA	
			SD, SE	0.0213, 0.0095	0.0099, 0.0014	
			MEDIAN	0.005	0.001	
			MIN, MAX	0.000, 0.051	0.000, 0.053	
			5%, 95%	0.000, 0.051	0.000, 0.025	
			# of BLQ/ALQ Values	1/0	21/0	
		At home combined	N	7	46	0.0239
			MEAN, GEO MEAN	0.021, NA	0.004, NA	
			SD, SE	0.0230, 0.0087	0.0064, 0.0009	
			MEDIAN	0.008	0.001	
			MIN, MAX	0.000, 0.053	0.000, 0.034	
			5%, 95%	0.000, 0.053	0.000, 0.015	
			# of BLQ/ALQ Values	1/0	21/0	
		Work	N	4	49	0.2825
			MEAN, GEO MEAN	0.007, NA	0.006, NA	
			SD, SE	0.0050, 0.0025	0.0118, 0.0017	
			MEDIAN	0.009	0.001	
			MIN, MAX	0.000, 0.011	0.000, 0.053	
			5%, 95%	0.000, 0.011	0.000, 0.034	
			# of BLQ/ALQ Values	1/0	21/0	
		Vehicles	N	2	51	0.9617
			MEAN, GEO MEAN	0.006, NA	0.006, NA	
			SD, SE	0.0078, 0.0055	0.0115, 0.0016	
			MEDIAN	0.006	0.002	
			MIN, MAX	0.000, 0.011	0.000, 0.053	
			5%, 95%	0.000, 0.011	0.000, 0.034	
			# of BLQ/ALQ Values	1/0	21/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438284

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 11 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 1	Harrogate Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)	Other places	N	19	34	0.1577
			MEAN, GEO MEAN	0.008, NA	0.005, NA	
			SD, SE	0.0132, 0.0030	0.0102, 0.0018	
			MEDIAN	0.003	0.001	
			MIN, MAX	0.000, 0.051	0.000, 0.053	
			5%, 95%	0.000, 0.051	0.000, 0.025	
			# of BLQ/ALQ Values	5/0	17/0	
		Away from home combined	N	23	30	0.1630
			MEAN, GEO MEAN	0.008, NA	0.005, NA	
			SD, SE	0.0122, 0.0025	0.0107, 0.0020	
			MEDIAN	0.003	0.001	
			MIN, MAX	0.000, 0.051	0.000, 0.053	
			5%, 95%	0.000, 0.034	0.000, 0.025	
			# of BLQ/ALQ Values	7/0	15/0	
	Harrogate Nicotine-N-glucuronide (nmol/mg Creatinine)	Spouse at home	N	2	60	0.3249
			MEAN, GEO MEAN	0.006, NA	0.002, NA	
			SD, SE	0.0085, 0.0060	0.0047, 0.0006	
			MEDIAN	0.006	0.000	
			MIN, MAX	0.000, 0.012	0.000, 0.023	
			5%, 95%	0.000, 0.012	0.000, 0.013	
			# of BLQ/ALQ Values	0/0	51/0	
		Others at home	N	5	57	0.0040
			MEAN, GEO MEAN	0.007, NA	0.002, NA	
			SD, SE	0.0084, 0.0037	0.0042, 0.0006	
			MEDIAN	0.004	0.000	
			MIN, MAX	0.000, 0.021	0.000, 0.023	
			5%, 95%	0.000, 0.021	0.000, 0.012	
			# of BLQ/ALQ Values	3/0	48/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438285

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 12 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 1	Harrogate Nicotine-N-glucuronide (nmol/mg Creatinine)	At home combined	N	7	55	0.0024
			MEAN, GEO MEAN	0.007, NA	0.001, NA	
			SD, SE	0.0077, 0.0029	0.0040, 0.0005	
			MEDIAN	0.004	0.000	
			MIN, MAX	0.000, 0.021	0.000, 0.023	
			5%, 95%	0.000, 0.021	0.000, 0.009	
			# of BLQ/ALQ Values	3/0	48/0	
		Work	N	4	58	0.0162
			MEAN, GEO MEAN	0.005, NA	0.002, NA	
			SD, SE	0.0037, 0.0018	0.0048, 0.0006	
			MEDIAN	0.005	0.000	
			MIN, MAX	0.000, 0.009	0.000, 0.023	
			5%, 95%	0.000, 0.009	0.000, 0.016	
			# of BLQ/ALQ Values	1/0	50/0	
		Vehicles	N	2	60	0.4843
			MEAN, GEO MEAN	0.002, NA	0.002, NA	
			SD, SE	0.0028, 0.0020	0.0048, 0.0006	
			MEDIAN	0.002	0.000	
			MIN, MAX	0.000, 0.004	0.000, 0.023	
			5%, 95%	0.000, 0.004	0.000, 0.014	
			# of BLQ/ALQ Values	1/0	50/0	
		Other places	N	20	42	0.3227
			MEAN, GEO MEAN	0.002, NA	0.002, NA	
			SD, SE	0.0051, 0.0011	0.0047, 0.0007	
			MEDIAN	0.000	0.000	
			MIN, MAX	0.000, 0.021	0.000, 0.023	
			5%, 95%	0.000, 0.015	0.000, 0.012	
			# of BLQ/ALQ Values	14/0	37/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438286

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 13 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 1	Harrogate Nicotine-N-glucuronide (nmol/mg Creatinine)	Away from home combined	N	24	38	0.1280
			MEAN, GEO MEAN	0.002, NA	0.002, NA	
			SD, SE	0.0048, 0.0010	0.0048, 0.0008	
			MEDIAN	0.000	0.000	
			MIN, MAX	0.000, 0.021	0.000, 0.023	
			5%, 95%	0.000, 0.009	0.000, 0.016	
			# of BLQ/ALQ Values	16/0	35/0	
	Harrogate Cotinine-N-glucuronide (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0334
			MEAN, GEO MEAN	0.038, 0.026	0.007, NA	
			SD, SE	0.0396, 0.0280	0.0161, 0.0020	
			MEDIAN	0.038	0.000	
			MIN, MAX	0.010, 0.066	0.000, 0.075	
			5%, 95%	0.010, 0.066	0.000, 0.049	
			# of BLQ/ALQ Values	0/0	49/0	
		Others at home	N	5	60	0.0681
			MEAN, GEO MEAN	0.027, NA	0.007, NA	
			SD, SE	0.0336, 0.0150	0.0149, 0.0019	
			MEDIAN	0.009	0.000	
			MIN, MAX	0.000, 0.075	0.000, 0.066	
			5%, 95%	0.000, 0.075	0.000, 0.046	
			# of BLQ/ALQ Values	3/0	46/0	
		At home combined	N	7	58	0.0057
			MEAN, GEO MEAN	0.030, NA	0.006, NA	
			SD, SE	0.0323, 0.0122	0.0129, 0.0017	
			MEDIAN	0.010	0.000	
			MIN, MAX	0.000, 0.075	0.000, 0.064	
			5%, 95%	0.000, 0.075	0.000, 0.036	
			# of BLQ/ALQ Values	3/0	46/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438287

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 14 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 1	Harrogate Cotinine-N-glucuronide (nmol/mg Creatinine)	Work	N	4	61	0.0876
			MEAN, GEO MEAN	0.017, NA	0.008, NA	
			SD, SE	0.0156, 0.0078	0.0175, 0.0022	
			MEDIAN	0.017	0.000	
			MIN, MAX	0.000, 0.036	0.000, 0.075	
			5%, 95%	0.000, 0.036	0.000, 0.055	
			# of BLQ/ALQ Values	1/0	48/0	
		Vehicles	N	2	63	0.8186
			MEAN, GEO MEAN	0.005, NA	0.008, NA	
			SD, SE	0.0071, 0.0050	0.0177, 0.0022	
			MEDIAN	0.005	0.000	
			MIN, MAX	0.000, 0.010	0.000, 0.075	
			5%, 95%	0.000, 0.010	0.000, 0.055	
			# of BLQ/ALQ Values	1/0	48/0	
		Other places	N	21	44	0.0245
			MEAN, GEO MEAN	0.012, NA	0.007, NA	
			SD, SE	0.0194, 0.0042	0.0165, 0.0025	
			MEDIAN	0.004	0.000	
			MIN, MAX	0.000, 0.075	0.000, 0.066	
			5%, 95%	0.000, 0.049	0.000, 0.055	
			# of BLQ/ALQ Values	13/0	36/0	
		Away from home combined	N	25	40	0.0152
			MEAN, GEO MEAN	0.012, NA	0.006, NA	
			SD, SE	0.0187, 0.0037	0.0165, 0.0026	
			MEDIAN	0.004	0.000	
			MIN, MAX	0.000, 0.075	0.000, 0.066	
			5%, 95%	0.000, 0.049	0.000, 0.060	
			# of BLQ/ALQ Values	15/0	34/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438288

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 15 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 2	Harrogate Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0536
			MEAN, GEO MEAN	0.176, 0.173	0.110, NA	
			SD, SE	0.0403, 0.0285	0.3723, 0.0469	
			MEDIAN	0.176	0.033	
			MIN, MAX	0.147, 0.204	0.000, 2.938	
			5%, 95%	0.147, 0.204	0.016, 0.209	
			# of BLQ/ALQ Values	0/0	0/0	
		Others at home	N	4	61	0.3297
			MEAN, GEO MEAN	0.105, 0.069	0.113, NA	
			SD, SE	0.0995, 0.0498	0.3780, 0.0484	
			MEDIAN	0.079	0.033	
			MIN, MAX	0.017, 0.243	0.000, 2.938	
			5%, 95%	0.017, 0.243	0.016, 0.204	
			# of BLQ/ALQ Values	0/0	0/0	
		At home combined	N	6	59	0.0486
			MEAN, GEO MEAN	0.128, 0.094	0.111, NA	
			SD, SE	0.0872, 0.0356	0.3843, 0.0500	
			MEDIAN	0.127	0.033	
			MIN, MAX	0.017, 0.243	0.000, 2.938	
			5%, 95%	0.017, 0.243	0.016, 0.209	
			# of BLQ/ALQ Values	0/0	0/0	
		Work	N	1	64	NA
			MEAN, GEO MEAN	0.209, 0.209	0.111, NA	
			SD, SE	NA, NA	0.3693, 0.0462	
			MEDIAN	0.209	0.033	
			MIN, MAX	0.209, 0.209	0.000, 2.938	
			5%, 95%	NA, NA	0.016, 0.204	
			# of BLQ/ALQ Values	0/0	0/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438289

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 16 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 2	Harrogate Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)	Vehicles	N	3	62	0.2510
			MEAN, GEO MEAN	0.094, 0.076	0.113, NA	
			SD, SE	0.0723, 0.0417	0.3753, 0.0477	
			MEDIAN	0.076	0.033	
			MIN, MAX	0.033, 0.174	0.000, 2.938	
			5%, 95%	0.033, 0.174	0.016, 0.209	
			# of BLQ/ALQ Values	0/0	0/0	
		Other places	N	20	45	0.0021
			MEAN, GEO MEAN	0.245, 0.084	0.053, NA	
			SD, SE	0.6463, 0.1445	0.0594, 0.0089	
			MEDIAN	0.075	0.033	
			MIN, MAX	0.016, 2.938	0.000, 0.243	
			5%, 95%	0.022, 1.772	0.016, 0.204	
			# of BLQ/ALQ Values	0/0	0/0	
		Away from home combined	N	23	42	0.0002
			MEAN, GEO MEAN	0.231, 0.087	0.047, NA	
			SD, SE	0.6024, 0.1256	0.0529, 0.0082	
			MEDIAN	0.076	0.030	
			MIN, MAX	0.016, 2.938	0.000, 0.243	
			5%, 95%	0.027, 0.606	0.016, 0.186	
			# of BLQ/ALQ Values	0/0	0/0	
	Harrogate Nicotine (nmol/mg Creatinine)	Spouse at home	N	2	63	0.2104
			MEAN, GEO MEAN	0.015, 0.015	0.040, NA	
			SD, SE	0.0042, 0.0030	0.2234, 0.0281	
			MEDIAN	0.015	0.006	
			MIN, MAX	0.012, 0.018	0.000, 1.782	
			5%, 95%	0.012, 0.018	0.000, 0.025	
			# of BLQ/ALQ Values	1/0	53/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438290

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 17 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 2	Harrogate Nicotine (nmol/mg Creatinine)	Others at home	N	4	61	0.2515
			MEAN, GEO MEAN	0.014, 0.012	0.041, NA	
			SD, SE	0.0057, 0.0029	0.2270, 0.0291	
			MEDIAN	0.015	0.006	
			MIN, MAX	0.006, 0.018	0.000, 1.782	
			5%, 95%	0.006, 0.018	0.000, 0.025	
			# of BLQ/ALQ Values	3/0	51/0	
		At home combined	N	6	59	0.0870
			MEAN, GEO MEAN	0.014, 0.013	0.041, NA	
			SD, SE	0.0049, 0.0020	0.2309, 0.0301	
			MEDIAN	0.015	0.006	
			MIN, MAX	0.006, 0.018	0.000, 1.782	
			5%, 95%	0.006, 0.018	0.000, 0.049	
			# of BLQ/ALQ Values	4/0	50/0	
		Work	N	1	64	NA
			MEAN, GEO MEAN	0.012, 0.012	0.039, NA	
			SD, SE	NA, NA	0.2216, 0.0277	
			MEDIAN	0.012	0.006	
			MIN, MAX	0.012, 0.012	0.000, 1.782	
			5%, 95%	NA, NA	0.000, 0.025	
			# of BLQ/ALQ Values	0/0	54/0	
		Vehicles	N	3	62	0.0425
			MEAN, GEO MEAN	0.026, 0.022	0.039, NA	
			SD, SE	0.0199, 0.0115	0.2252, 0.0286	
			MEDIAN	0.018	0.006	
			MIN, MAX	0.012, 0.049	0.000, 1.782	
			5%, 95%	0.012, 0.049	0.000, 0.025	
			# of BLQ/ALQ Values	1/0	53/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438291

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 18 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 2	Harrogate Nicotine (nmol/mg Creatinine)	Other places	N	20	45	0.1713
			MEAN, GEO MEAN	0.104, NA	0.010, NA	
			SD, SE	0.3954, 0.0884	0.0063, 0.0009	
			MEDIAN	0.012	0.006	
			MIN, MAX	0.000, 1.782	0.000, 0.025	
			5%, 95%	0.003, 0.934	0.000, 0.025	
			# of BLQ/ALQ Values	13/0	41/0	
		Away from home combined	N	23	42	0.0550
			MEAN, GEO MEAN	0.092, NA	0.010, NA	
			SD, SE	0.3687, 0.0769	0.0064, 0.0010	
			MEDIAN	0.012	0.006	
			MIN, MAX	0.000, 1.782	0.000, 0.025	
			5%, 95%	0.006, 0.086	0.000, 0.025	
			# of BLQ/ALQ Values	14/0	40/0	
	Harrogate Cotinine (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0247
			MEAN, GEO MEAN	0.034, 0.033	0.016, NA	
			SD, SE	0.0085, 0.0060	0.0402, 0.0051	
			MEDIAN	0.034	0.011	
			MIN, MAX	0.028, 0.040	0.000, 0.323	
			5%, 95%	0.028, 0.040	0.000, 0.028	
			# of BLQ/ALQ Values	0/0	47/0	
		Others at home	N	4	61	0.2778
			MEAN, GEO MEAN	0.019, 0.015	0.017, NA	
			SD, SE	0.0150, 0.0075	0.0408, 0.0052	
			MEDIAN	0.014	0.011	
			MIN, MAX	0.006, 0.040	0.000, 0.323	
			5%, 95%	0.006, 0.040	0.000, 0.028	
			# of BLQ/ALQ Values	2/0	45/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438292

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 19 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 2	Harrogate Cotinine (nmol/mg Creatinine)	At home combined	N	6	59	0.0243
			MEAN, GEO MEAN	0.024, 0.019	0.016, NA	
			SD, SE	0.0146, 0.0060	0.0414, 0.0054	
			MEDIAN	0.023	0.006	
			MIN, MAX	0.006, 0.040	0.000, 0.323	
			5%, 95%	0.006, 0.040	0.000, 0.028	
			# of BLQ/ALQ Values	2/0	45/0	
		Work	N	1	64	NA
			MEAN, GEO MEAN	0.011, 0.011	0.017, NA	
			SD, SE	NA, NA	0.0400, 0.0050	
			MEDIAN	0.011	0.011	
			MIN, MAX	0.011, 0.011	0.000, 0.323	
			5%, 95%	NA, NA	0.000, 0.040	
			# of BLQ/ALQ Values	0/0	47/0	
		Vehicles	N	3	62	0.1283
			MEAN, GEO MEAN	0.017, 0.016	0.017, NA	
			SD, SE	0.0060, 0.0035	0.0406, 0.0052	
			MEDIAN	0.017	0.009	
			MIN, MAX	0.011, 0.023	0.000, 0.323	
			5%, 95%	0.011, 0.023	0.000, 0.040	
			# of BLQ/ALQ Values	1/0	46/0	
		Other places	N	20	45	0.0388
			MEAN, GEO MEAN	0.029, NA	0.011, NA	
			SD, SE	0.0697, 0.0156	0.0093, 0.0014	
			MEDIAN	0.011	0.006	
			MIN, MAX	0.000, 0.323	0.000, 0.040	
			5%, 95%	0.003, 0.182	0.000, 0.028	
			# of BLQ/ALQ Values	9/0	38/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438293

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 20 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 2	Harrogate Cotinine (nmol/mg Creatinine)	Away from home combined	N	23	42	0.0123
			MEAN, GEO MEAN	0.027, NA	0.011, NA	
			SD, SE	0.0650, 0.0136	0.0095, 0.0015	
			MEDIAN	0.011	0.006	
			MIN, MAX	0.000, 0.323	0.000, 0.040	
			5%, 95%	0.006, 0.040	0.000, 0.028	
			# of BLQ/ALQ Values	10/0	37/0	
	Harrogate Trans-3-hydroxycotinine (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0398
			MEAN, GEO MEAN	0.089, 0.088	0.031, NA	
			SD, SE	0.0148, 0.0105	0.0642, 0.0081	
			MEDIAN	0.089	0.010	
			MIN, MAX	0.078, 0.099	0.000, 0.411	
			5%, 95%	0.078, 0.099	0.005, 0.099	
			# of BLQ/ALQ Values	0/0	17/0	
		Others at home	N	4	61	0.4685
			MEAN, GEO MEAN	0.037, 0.021	0.032, NA	
			SD, SE	0.0425, 0.0213	0.0654, 0.0084	
			MEDIAN	0.021	0.010	
		At home combined	N	6	59	0.0658
			MEAN, GEO MEAN	0.054, 0.034	0.030, NA	
			SD, SE	0.0430, 0.0176	0.0657, 0.0086	
			MEDIAN	0.052	0.010	
			MIN, MAX	0.005, 0.099	0.000, 0.411	
			5%, 95%	0.005, 0.099	0.005, 0.109	
			# of BLQ/ALQ Values	1/0	16/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438294

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 21 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 2	Harrogate Trans-3-hydroxycotinine (nmol/mg Creatinine)	Work	N	1	64	NA
			MEAN, GEO MEAN	0.109, 0.109	0.031, NA	
			SD, SE	NA, NA	0.0638, 0.0080	
			MEDIAN	0.109	0.010	
			MIN, MAX	0.109, 0.109	0.000, 0.411	
			5%, 95%	NA, NA	0.005, 0.099	
			# of BLQ/ALQ Values	0/0	17/0	
		Vehicles	N	3	62	0.7374
			MEAN, GEO MEAN	0.024, 0.017	0.033, NA	
			SD, SE	0.0242, 0.0140	0.0654, 0.0083	
			MEDIAN	0.010	0.010	
			MIN, MAX	0.010, 0.052	0.000, 0.411	
			5%, 95%	0.010, 0.052	0.005, 0.099	
			# of BLQ/ALQ Values	1/0	16/0	
		Other places	N	20	45	0.0056
			MEAN, GEO MEAN	0.061, 0.027	0.020, NA	
			SD, SE	0.1050, 0.0235	0.0256, 0.0038	
			MEDIAN	0.021	0.010	
			MIN, MAX	0.005, 0.411	0.000, 0.109	
			5%, 95%	0.008, 0.354	0.005, 0.099	
			# of BLQ/ALQ Values	4/0	13/0	
		Away from home combined	N	23	42	0.0009
			MEAN, GEO MEAN	0.061, 0.028	0.017, NA	
			SD, SE	0.0988, 0.0206	0.0217, 0.0034	
			MEDIAN	0.021	0.010	
			MIN, MAX	0.005, 0.411	0.000, 0.099	
			5%, 95%	0.010, 0.297	0.005, 0.062	
			# of BLQ/ALQ Values	5/0	12/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438295

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 22 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 2	Harrugate Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)	Spouse at home	N	1	58	NA
			MEAN, GEO MEAN	0.035, 0.035	0.009, NA	
			SD, SE	NA, NA	0.0187, 0.0024	
			MEDIAN	0.035	0.001	
			MIN, MAX	0.035, 0.035	0.000, 0.105	
			5%, 95%	NA, NA	0.000, 0.053	
			# of BLQ/ALQ Values	0/0	17/0	
		Others at home	N	4	55	0.4888
			MEAN, GEO MEAN	0.013, NA	0.009, NA	
			SD, SE	0.0191, 0.0096	0.0189, 0.0026	
			MEDIAN	0.005	0.001	
			MIN, MAX	0.000, 0.041	0.000, 0.105	
			5%, 95%	0.000, 0.041	0.000, 0.053	
			# of BLQ/ALQ Values	1/0	16/0	
		At home combined	N	5	54	0.1872
			MEAN, GEO MEAN	0.017, NA	0.008, NA	
			SD, SE	0.0193, 0.0086	0.0188, 0.0026	
			MEDIAN	0.008	0.001	
			MIN, MAX	0.000, 0.041	0.000, 0.105	
			5%, 95%	0.000, 0.041	0.000, 0.053	
			# of BLQ/ALQ Values	1/0	16/0	
		Work	N	1	58	NA
			MEAN, GEO MEAN	0.029, 0.029	0.009, NA	
			SD, SE	NA, NA	0.0188, 0.0025	
			MEDIAN	0.029	0.001	
			MIN, MAX	0.029, 0.029	0.000, 0.105	
			5%, 95%	NA, NA	0.000, 0.053	
			# of BLQ/ALQ Values	0/0	17/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438296

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 23 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 2	Harrogate Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)	Vehicles	N	3	56	0.9719
			MEAN, GEO MEAN	0.018, NA	0.009, NA	
			SD, SE	0.0303, 0.0175	0.0183, 0.0024	
			MEDIAN	0.001	0.001	
			MIN, MAX	0.000, 0.053	0.000, 0.105	
			5%, 95%	0.000, 0.053	0.000, 0.041	
			# of BLQ/ALQ Values	1/0	16/0	
		Other places	N	18	41	0.1658
			MEAN, GEO MEAN	0.015, NA	0.007, NA	
			SD, SE	0.0283, 0.0067	0.0123, 0.0019	
			MEDIAN	0.004	0.001	
			MIN, MAX	0.000, 0.105	0.000, 0.053	
			5%, 95%	0.000, 0.105	0.000, 0.035	
			# of BLQ/ALQ Values	4/0	13/0	
		Away from home combined	N	21	38	0.0387
			MEAN, GEO MEAN	0.017, NA	0.005, NA	
			SD, SE	0.0278, 0.0061	0.0093, 0.0015	
			MEDIAN	0.004	0.001	
			MIN, MAX	0.000, 0.105	0.000, 0.041	
			5%, 95%	0.000, 0.072	0.000, 0.035	
			# of BLQ/ALQ Values	5/0	12/0	
	Harrogate Nicotine-N-glucuronide (nmol/mg Creatinine)	Spouse at home	N	2	61	0.0109
			MEAN, GEO MEAN	0.004, 0.003	0.006, NA	
			SD, SE	0.0007, 0.0005	0.0346, 0.0044	
			MEDIAN	0.004	0.000	
			MIN, MAX	0.003, 0.004	0.000, 0.270	
			5%, 95%	0.003, 0.004	0.000, 0.011	
			# of BLQ/ALQ Values	1/0	53/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438297

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 24 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 2	Harrogate Nicotine-N-glucuronide (nmol/mg Creatinine)	Others at home	N	4	59	0.1180
			MEAN, GEO MEAN	0.005, NA	0.006, NA	
			SD, SE	0.0076, 0.0038	0.0351, 0.0046	
			MEDIAN	0.002	0.000	
			MIN, MAX	0.000, 0.016	0.000, 0.270	
			5%, 95%	0.000, 0.016	0.000, 0.011	
			# of BLQ/ALQ Values	3/0	51/0	
		At home combined	N	6	57	0.0046
			MEAN, GEO MEAN	0.004, NA	0.006, NA	
			SD, SE	0.0060, 0.0024	0.0358, 0.0047	
			MEDIAN	0.003	0.000	
			MIN, MAX	0.000, 0.016	0.000, 0.270	
			5%, 95%	0.000, 0.016	0.000, 0.011	
			# of BLQ/ALQ Values	4/0	50/0	
		Work	N	1	62	NA
			MEAN, GEO MEAN	0.005, 0.005	0.006, NA	
			SD, SE	NA, NA	0.0343, 0.0044	
			MEDIAN	0.005	0.000	
			MIN, MAX	0.005, 0.005	0.000, 0.270	
			5%, 95%	NA, NA	0.000, 0.011	
			# of BLQ/ALQ Values	0/0	54/0	
		Vehicles	N	2	61	0.3307
			MEAN, GEO MEAN	0.002, NA	0.006, NA	
			SD, SE	0.0028, 0.0020	0.0346, 0.0044	
			MEDIAN	0.002	0.000	
			MIN, MAX	0.000, 0.004	0.000, 0.270	
			5%, 95%	0.000, 0.004	0.000, 0.011	
			# of BLQ/ALQ Values	1/0	53/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438298

Final Draft: 22 October 2003

Page 329 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 25 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 2	Harrogate Nicotine-N-glucuronide (nmol/mg Creatinine)	Other places	N	18	45	0.0562
			MEAN, GEO MEAN	0.017, NA	0.001, NA	
			SD, SE	0.0633, 0.0149	0.0028, 0.0004	
			MEDIAN	0.000	0.000	
			MIN, MAX	0.000, 0.270	0.000, 0.016	
			5%, 95%	0.000, 0.270	0.000, 0.005	
			# of BLQ/ALQ Values	13/0	41/0	
		Away from home combined	N	21	42	0.0063
			MEAN, GEO MEAN	0.015, NA	0.001, NA	
			SD, SE	0.0585, 0.0128	0.0028, 0.0004	
			MEDIAN	0.000	0.000	
			MIN, MAX	0.000, 0.270	0.000, 0.016	
			5%, 95%	0.000, 0.017	0.000, 0.003	
			# of BLQ/ALQ Values	14/0	40/0	
	Harrogate Cotinine-N-glucuronide (nmol/mg Creatinine)	Spouse at home	N	2	63	0.1750
			MEAN, GEO MEAN	0.014, 0.013	0.011, NA	
			SD, SE	0.0049, 0.0035	0.0273, 0.0034	
			MEDIAN	0.014	0.000	
			MIN, MAX	0.010, 0.017	0.000, 0.195	
			5%, 95%	0.010, 0.017	0.000, 0.043	
			# of BLQ/ALQ Values	0/0	47/0	
		Others at home	N	4	61	0.2109
			MEAN, GEO MEAN	0.021, NA	0.010, NA	
			SD, SE	0.0241, 0.0120	0.0271, 0.0035	
			MEDIAN	0.020	0.000	
			MIN, MAX	0.000, 0.045	0.000, 0.195	
			5%, 95%	0.000, 0.045	0.000, 0.038	
			# of BLQ/ALQ Values	2/0	45/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438299

Final Draft: 22 October 2003

Page 330 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 26 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 2	Harrogate Cotinine-N-glucuronide (nmol/mg Creatinine)	At home combined	N	6	59	0.0629
			MEAN, GEO MEAN	0.019, NA	0.010, NA	
			SD, SE	0.0192, 0.0078	0.0275, 0.0036	
			MEDIAN	0.014	0.000	
			MIN, MAX	0.000, 0.045	0.000, 0.195	
			5%, 95%	0.000, 0.045	0.000, 0.043	
			# of BLQ/ALQ Values	2/0	45/0	
		Work	N	1	64	NA
			MEAN, GEO MEAN	0.043, 0.043	0.010, NA	
			SD, SE	NA, NA	0.0268, 0.0033	
			MEDIAN	0.043	0.001	
			MIN, MAX	0.043, 0.043	0.000, 0.195	
			5%, 95%	NA, NA	0.000, 0.039	
			# of BLQ/ALQ Values	0/0	47/0	
		Vehicles	N	3	62	0.6528
			MEAN, GEO MEAN	0.008, NA	0.011, NA	
			SD, SE	0.0100, 0.0058	0.0274, 0.0035	
			MEDIAN	0.004	0.001	
			MIN, MAX	0.000, 0.019	0.000, 0.195	
			5%, 95%	0.000, 0.019	0.000, 0.043	
			# of BLQ/ALQ Values	1/0	46/0	
		Other places	N	20	45	0.0010
			MEAN, GEO MEAN	0.022, NA	0.006, NA	
			SD, SE	0.0425, 0.0095	0.0140, 0.0021	
			MEDIAN	0.011	0.000	
			MIN, MAX	0.000, 0.195	0.000, 0.058	
			5%, 95%	0.000, 0.117	0.000, 0.043	
			# of BLQ/ALQ Values	9/0	38/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438300

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 27 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 2	Harrogate Cotinine-N-glucuronide (nmol/mg Creatinine)	Away from home combined	N	23	42	0.0003
			MEAN, GEO MEAN	0.021, NA	0.005, NA	
			SD, SE	0.0400, 0.0083	0.0131, 0.0020	
			MEDIAN	0.013	0.000	
			MIN, MAX	0.000, 0.195	0.000, 0.058	
			5%, 95%	0.000, 0.043	0.000, 0.039	
			# of BLQ/ALQ Values	10/0	37/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438301

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 28 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 3	Harrogate Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0199
			MEAN, GEO MEAN	0.322, 0.286	0.049, 0.036	
			SD, SE	0.2093, 0.1480	0.0500, 0.0063	
			MEDIAN	0.322	0.033	
			MIN, MAX	0.174, 0.470	0.011, 0.283	
			5%, 95%	0.174, 0.470	0.017, 0.109	
			# of BLQ/ALQ Values	0/0	0/0	
		Others at home	N	1	64	NA
			MEAN, GEO MEAN	0.094, 0.094	0.056, 0.038	
			SD, SE	NA, NA	0.0738, 0.0092	
			MEDIAN	0.094	0.033	
			MIN, MAX	0.094, 0.094	0.011, 0.470	
			5%, 95%	NA, NA	0.017, 0.174	
			# of BLQ/ALQ Values	0/0	0/0	
		At home combined	N	3	62	0.0068
			MEAN, GEO MEAN	0.246, 0.197	0.048, 0.036	
			SD, SE	0.1981, 0.1144	0.0501, 0.0064	
			MEDIAN	0.174	0.033	
			MIN, MAX	0.094, 0.470	0.011, 0.283	
			5%, 95%	0.094, 0.470	0.017, 0.109	
			# of BLQ/ALQ Values	0/0	0/0	
		Work	N	5	60	0.2782
			MEAN, GEO MEAN	0.064, 0.053	0.056, 0.038	
			SD, SE	0.0367, 0.0164	0.0757, 0.0098	
			MEDIAN	0.051	0.033	
			MIN, MAX	0.016, 0.109	0.011, 0.470	
			5%, 95%	0.016, 0.109	0.017, 0.224	
			# of BLQ/ALQ Values	0/0	0/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438302

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 29 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 3	Harrogate Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)	Vehicles	N	1	64	NA
			MEAN, GEO MEAN	0.470, 0.470	0.050, 0.037	
			SD, SE	NA, NA	0.0521, 0.0065	
			MEDIAN	0.470	0.033	
			MIN, MAX	0.470, 0.470	0.011, 0.283	
			5%, 95%	NA, NA	0.017, 0.139	
			# of BLQ/ALQ Values	0/0	0/0	
		Other places	N	10	55	0.1408
			MEAN, GEO MEAN	0.082, 0.056	0.052, 0.036	
			SD, SE	0.0811, 0.0256	0.0717, 0.0097	
			MEDIAN	0.062	0.033	
			MIN, MAX	0.017, 0.283	0.011, 0.470	
			5%, 95%	0.017, 0.283	0.017, 0.174	
			# of BLQ/ALQ Values	0/0	0/0	
		Away from home combined	N	15	50	0.0420
			MEAN, GEO MEAN	0.100, 0.061	0.044, 0.034	
			SD, SE	0.1228, 0.0317	0.0444, 0.0063	
			MEDIAN	0.054	0.033	
			MIN, MAX	0.016, 0.470	0.011, 0.274	
			5%, 95%	0.016, 0.470	0.017, 0.107	
			# of BLQ/ALQ Values	0/0	0/0	
	Harrogate Nicotine (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0204
			MEAN, GEO MEAN	0.034, 0.030	0.010, NA	
			SD, SE	0.0219, 0.0155	0.0059, 0.0007	
			MEDIAN	0.034	0.006	
			MIN, MAX	0.018, 0.049	0.000, 0.031	
			5%, 95%	0.018, 0.049	0.000, 0.018	
			# of BLQ/ALQ Values	0/0	57/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438303

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 30 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 3	Harrogate Nicotine (nmol/mg Creatinine)	Others at home	N	1	64	NA
			MEAN, GEO MEAN	0.012, 0.012	0.010, NA	
			SD, SE	NA, NA	0.0077, 0.0010	
			MEDIAN	0.012	0.006	
			MIN, MAX	0.012, 0.012	0.000, 0.049	
			5%, 95%	NA, NA	0.000, 0.025	
			# of BLQ/ALQ Values	1/0	56/0	
		At home combined	N	3	62	0.0218
			MEAN, GEO MEAN	0.026, 0.022	0.010, NA	
			SD, SE	0.0199, 0.0115	0.0059, 0.0008	
			MEDIAN	0.018	0.006	
			MIN, MAX	0.012, 0.049	0.000, 0.031	
			5%, 95%	0.012, 0.049	0.000, 0.018	
			# of BLQ/ALQ Values	1/0	56/0	
		Work	N	5	60	0.4444
			MEAN, GEO MEAN	0.011, NA	0.010, NA	
			SD, SE	0.0056, 0.0029	0.0078, 0.0010	
			MEDIAN	0.012	0.006	
			MIN, MAX	0.000, 0.018	0.000, 0.049	
			5%, 95%	0.000, 0.018	0.003, 0.025	
			# of BLQ/ALQ Values	3/0	54/0	
		Vehicles	N	1	64	NA
			MEAN, GEO MEAN	0.049, 0.049	0.010, NA	
			SD, SE	NA, NA	0.0059, 0.0007	
			MEDIAN	0.049	0.006	
			MIN, MAX	0.049, 0.049	0.000, 0.031	
			5%, 95%	NA, NA	0.000, 0.018	
			# of BLQ/ALQ Values	0/0	57/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438304

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 31 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 3	Harrogate Nicotine (nmol/mg Creatinine)	Other places	N	10	55	0.1216
			MEAN, GEO MEAN	0.007, NA	0.011, NA	
			SD, SE	0.0038, 0.0012	0.0080, 0.0011	
			MEDIAN	0.006	0.012	
			MIN, MAX	0.000, 0.012	0.000, 0.049	
			5%, 95%	0.000, 0.012	0.000, 0.025	
			# of BLQ/ALQ Values	9/0	48/0	
		Away from home combined	N	15	50	0.6227
			MEAN, GEO MEAN	0.011, NA	0.010, NA	
			SD, SE	0.0116, 0.0030	0.0061, 0.0009	
			MEDIAN	0.006	0.009	
			MIN, MAX	0.000, 0.049	0.000, 0.031	
			5%, 95%	0.000, 0.049	0.006, 0.025	
			# of BLQ/ALQ Values	11/0	46/0	
	Harrogate Cotinine (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0146
			MEAN, GEO MEAN	0.054, 0.047	0.011, NA	
			SD, SE	0.0361, 0.0255	0.0090, 0.0011	
			MEDIAN	0.054	0.006	
			MIN, MAX	0.028, 0.079	0.000, 0.051	
			5%, 95%	0.028, 0.079	0.006, 0.023	
			# of BLQ/ALQ Values	0/0	50/0	
		Others at home	N	1	64	NA
			MEAN, GEO MEAN	0.011, 0.011	0.012, NA	
			SD, SE	NA, NA	0.0125, 0.0016	
			MEDIAN	0.011	0.009	
			MIN, MAX	0.011, 0.011	0.000, 0.079	
			5%, 95%	NA, NA	0.006, 0.028	
			# of BLQ/ALQ Values	0/0	50/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438305

Final Draft: 22 October 2003

Page 336 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 32 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 3	Harrogate Cotinine (nmol/mg Creatinine)	At home combined	N	3	62	0.0200
			MEAN, GEO MEAN	0.039, 0.029	0.011, NA	
			SD, SE	0.0354, 0.0204	0.0090, 0.0011	
			MEDIAN	0.028	0.006	
			MIN, MAX	0.011, 0.079	0.000, 0.051	
			5%, 95%	0.011, 0.079	0.006, 0.023	
			# of BLQ/ALQ Values	0/0	50/0	
		Work	N	5	60	0.8536
			MEAN, GEO MEAN	0.010, NA	0.012, NA	
			SD, SE	0.0073, 0.0033	0.0127, 0.0016	
			MEDIAN	0.011	0.009	
			MIN, MAX	0.000, 0.017	0.000, 0.079	
			5%, 95%	0.000, 0.017	0.006, 0.040	
			# of BLQ/ALQ Values	3/0	47/0	
		Vehicles	N	1	64	NA
			MEAN, GEO MEAN	0.079, 0.079	0.011, NA	
			SD, SE	NA, NA	0.0091, 0.0011	
			MEDIAN	0.079	0.009	
			MIN, MAX	0.079, 0.079	0.000, 0.051	
			5%, 95%	NA, NA	0.006, 0.028	
			# of BLQ/ALQ Values	0/0	50/0	
		Other places	N	10	55	0.7480
			MEAN, GEO MEAN	0.014, 0.010	0.012, NA	
			SD, SE	0.0138, 0.0044	0.0122, 0.0016	
			MEDIAN	0.009	0.011	
			MIN, MAX	0.006, 0.051	0.000, 0.079	
			5%, 95%	0.006, 0.051	0.006, 0.028	
			# of BLQ/ALQ Values	5/0	45/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438306

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 33 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 3	Harrogate Cotinine (nmol/mg Creatinine)	Away from home combined	N	15	50	0.4381
			MEAN, GEO MEAN	0.017, NA	0.011, NA	
			SD, SE	0.0209, 0.0054	0.0081, 0.0012	
			MEDIAN	0.011	0.009	
			MIN, MAX	0.000, 0.079	0.000, 0.051	
			5%, 95%	0.000, 0.079	0.006, 0.028	
			# of BLQ/ALQ Values	7/0	43/0	
	Harrogate Trans-3-hydroxycotinine (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0178
			MEAN, GEO MEAN	0.151, 0.137	0.018, 0.012	
			SD, SE	0.0884, 0.0625	0.0203, 0.0026	
			MEDIAN	0.151	0.010	
			MIN, MAX	0.088, 0.213	0.005, 0.114	
			5%, 95%	0.088, 0.213	0.005, 0.042	
			# of BLQ/ALQ Values	0/0	30/0	
		Others at home	N	1	64	NA
			MEAN, GEO MEAN	0.026, 0.026	0.022, 0.013	
			SD, SE	NA, NA	0.0328, 0.0041	
			MEDIAN	0.026	0.010	
		At home combined	N	3	62	0.0104
			MEAN, GEO MEAN	0.109, 0.079	0.018, 0.012	
			SD, SE	0.0953, 0.0550	0.0205, 0.0026	
			MEDIAN	0.088	0.010	
			MIN, MAX	0.026, 0.213	0.005, 0.114	
			5%, 95%	0.026, 0.213	0.005, 0.042	
			# of BLQ/ALQ Values	0/0	30/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438307

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 34 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 3	Harrogate Trans-3-hydroxycentinine (nmol/mg Creatinine)	Work	N	5	60	0.5174
			MEAN, GEO MEAN	0.019, 0.015	0.022, 0.013	
			SD, SE	0.0125, 0.0056	0.0337, 0.0043	
			MEDIAN	0.016	0.010	
			MIN, MAX	0.005, 0.036	0.005, 0.213	
			5%, 95%	0.005, 0.036	0.005, 0.091	
			# of BLQ/ALQ Values	0/0	30/0	
		Vehicles	N	1	64	NA
			MEAN, GEO MEAN	0.213, 0.213	0.019, 0.012	
			SD, SE	NA, NA	0.0220, 0.0028	
			MEDIAN	0.213	0.010	
			MIN, MAX	0.213, 0.213	0.005, 0.114	
			5%, 95%	NA, NA	0.005, 0.073	
			# of BLQ/ALQ Values	0/0	30/0	
		Other places	N	10	55	0.0410
			MEAN, GEO MEAN	0.035, 0.023	0.019, 0.012	
			SD, SE	0.0346, 0.0109	0.0319, 0.0043	
			MEDIAN	0.024	0.010	
			MIN, MAX	0.005, 0.114	0.005, 0.213	
			5%, 95%	0.005, 0.114	0.005, 0.088	
			# of BLQ/ALQ Values	0/0	30/0	
		Away from home combined	N	15	50	0.0208
			MEAN, GEO MEAN	0.041, 0.022	0.016, 0.011	
			SD, SE	0.0560, 0.0145	0.0183, 0.0026	
			MEDIAN	0.021	0.010	
			MIN, MAX	0.005, 0.213	0.005, 0.094	
			5%, 95%	0.005, 0.213	0.005, 0.042	
			# of BLQ/ALQ Values	0/0	30/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438308

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 35 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 3	Harrogate Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)	Spouse at home	N	2	59	0.0172
			MEAN, GEO MEAN	0.035, 0.031	0.004, NA	
			SD, SE	0.0219, 0.0155	0.0082, 0.0011	
			MEDIAN	0.035	0.001	
			MIN, MAX	0.019, 0.050	0.000, 0.040	
			5%, 95%	0.019, 0.050	0.000, 0.030	
			# of BLQ/ALQ Values	0/0	30/0	
		Others at home	N	1	60	NA
			MEAN, GEO MEAN	0.012, 0.012	0.005, NA	
			SD, SE	NA, NA	0.0102, 0.0013	
			MEDIAN	0.012	0.001	
			MIN, MAX	0.012, 0.012	0.000, 0.050	
			5%, 95%	NA, NA	0.000, 0.032	
			# of BLQ/ALQ Values	0/0	30/0	
		At home combined	N	3	58	0.0052
			MEAN, GEO MEAN	0.027, 0.023	0.004, NA	
			SD, SE	0.0202, 0.0117	0.0082, 0.0011	
			MEDIAN	0.019	0.001	
			MIN, MAX	0.012, 0.050	0.000, 0.040	
			5%, 95%	0.012, 0.050	0.000, 0.030	
			# of BLQ/ALQ Values	0/0	30/0	
		Work	N	4	57	0.1555
			MEAN, GEO MEAN	0.006, 0.003	0.005, NA	
			SD, SE	0.0080, 0.0040	0.0103, 0.0014	
			MEDIAN	0.003	0.000	
			MIN, MAX	0.001, 0.018	0.000, 0.050	
			5%, 95%	0.001, 0.018	0.000, 0.034	
			# of BLQ/ALQ Values	0/0	30/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438309

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 36 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 3	Hemgate Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)	Vehicles	N	1	60	NA
			MEAN, GEO MEAN	0.050, 0.050	0.004, NA	
			SD, SE	NA, NA	0.0083, 0.0011	
			MEDIAN	0.050	0.001	
			MIN, MAX	0.050, 0.050	0.000, 0.040	
			5%, 95%	NA, NA	0.000, 0.025	
			# of BLQ/ALQ Values	0/0	30/0	
		Other places	N	9	52	0.0022
			MEAN, GEO MEAN	0.012, NA	0.004, NA	
			SD, SE	0.0125, 0.0042	0.0092, 0.0013	
			MEDIAN	0.009	0.000	
			MIN, MAX	0.000, 0.034	0.000, 0.050	
			5%, 95%	0.000, 0.034	0.000, 0.019	
			# of BLQ/ALQ Values	0/0	30/0	
		Away from home combined	N	13	48	0.0003
			MEAN, GEO MEAN	0.013, NA	0.003, NA	
			SD, SE	0.0158, 0.0044	0.0067, 0.0010	
			MEDIAN	0.004	0.000	
			MIN, MAX	0.000, 0.050	0.000, 0.040	
			5%, 95%	0.000, 0.050	0.000, 0.012	
			# of BLQ/ALQ Values	0/0	30/0	
	Hemgate Nicotine-N-glucuronide (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0065
			MEAN, GEO MEAN	0.012, 0.006	0.001, NA	
			SD, SE	0.0134, 0.0095	0.0024, 0.0003	
			MEDIAN	0.012	0.000	
			MIN, MAX	0.002, 0.021	0.000, 0.011	
			5%, 95%	0.002, 0.021	0.000, 0.006	
			# of BLQ/ALQ Values	0/0	57/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438310

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 37 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 3	Harrogate Nicotine-N-glucuronide (nmol/mg Creatinine)	Others at home	N	1	64	NA
			MEAN, GEO MEAN	0.004, 0.004	0.001, NA	
			SD, SE	NA, NA	0.0034, 0.0004	
			MEDIAN	0.004	0.000	
			MIN, MAX	0.004, 0.004	0.000, 0.021	
			5%, 95%	NA, NA	0.000, 0.008	
			# of BLQ/ALQ Values	1/0	56/0	
		At home combined	N	3	62	0.0009
			MEAN, GEO MEAN	0.009, 0.006	0.001, NA	
			SD, SE	0.0104, 0.0060	0.0024, 0.0003	
			MEDIAN	0.004	0.000	
			MIN, MAX	0.002, 0.021	0.000, 0.011	
			5%, 95%	0.002, 0.021	0.000, 0.006	
			# of BLQ/ALQ Values	1/0	56/0	
		Work	N	5	60	0.2113
			MEAN, GEO MEAN	0.003, NA	0.001, NA	
			SD, SE	0.0050, 0.0022	0.0033, 0.0004	
			MEDIAN	0.000	0.000	
			MIN, MAX	0.000, 0.011	0.000, 0.021	
			5%, 95%	0.000, 0.011	0.000, 0.007	
			# of BLQ/ALQ Values	3/0	54/0	
		Vehicles	N	1	64	NA
			MEAN, GEO MEAN	0.021, 0.021	0.001, NA	
			SD, SE	NA, NA	0.0024, 0.0003	
			MEDIAN	0.021	0.000	
			MIN, MAX	0.021, 0.021	0.000, 0.011	
			5%, 95%	NA, NA	0.000, 0.006	
			# of BLQ/ALQ Values	0/0	57/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438311

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 38 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 3	Harrogate Nicotine-N-glucuronide (nmol/mg Creatinine)	Other places	N	10	55	0.1390
			MEAN, GEO MEAN	0.002, NA	0.001, NA	
			SD, SE	0.0026, 0.0008	0.0036, 0.0005	
			MEDIAN	0.000	0.000	
			MIN, MAX	0.000, 0.006	0.000, 0.021	
			5%, 95%	0.000, 0.006	0.000, 0.008	
			# of BLQ/ALQ Values	9/0	48/0	
		Away from home combined	N	15	50	0.0036
			MEAN, GEO MEAN	0.004, NA	0.001, NA	
			SD, SE	0.0058, 0.0015	0.0017, 0.0002	
			MEDIAN	0.000	0.000	
			MIN, MAX	0.000, 0.021	0.000, 0.008	
			5%, 95%	0.000, 0.021	0.000, 0.004	
			# of BLQ/ALQ Values	11/0	46/0	
	Harrogate Cotinine-N-glucuronide (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0298
			MEAN, GEO MEAN	0.034, 0.024	0.006, NA	
			SD, SE	0.0332, 0.0235	0.0131, 0.0016	
			MEDIAN	0.034	0.000	
			MIN, MAX	0.010, 0.057	0.000, 0.067	
			5%, 95%	0.010, 0.057	0.000, 0.028	
			# of BLQ/ALQ Values	0/0	50/0	
		Others at home	N	1	64	NA
			MEAN, GEO MEAN	0.027, 0.027	0.006, NA	
			SD, SE	NA, NA	0.0142, 0.0018	
			MEDIAN	0.027	0.000	
			MIN, MAX	0.027, 0.027	0.000, 0.067	
			5%, 95%	NA, NA	0.000, 0.035	
			# of BLQ/ALQ Values	0/0	50/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438312

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1 4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 39 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 3	Harrogate Cotinine-N-glucuronide (nmol/mg Creatinine)	At home combined	N	3	62	0.0057
			MEAN, GEO MEAN	0.031, 0.025	0.005, NA	
			SD, SE	0.0238, 0.0137	0.0129, 0.0016	
			MEDIAN	0.027	0.000	
			MIN, MAX	0.010, 0.057	0.000, 0.067	
			5%, 95%	0.010, 0.057	0.000, 0.028	
			# of BLQ/ALQ Values	0/0	50/0	
		Work	N	5	60	0.0341
			MEAN, GEO MEAN	0.014, NA	0.006, NA	
			SD, SE	0.0148, 0.0066	0.0143, 0.0018	
			MEDIAN	0.011	0.000	
			MIN, MAX	0.000, 0.035	0.000, 0.067	
			5%, 95%	0.000, 0.035	0.000, 0.043	
			# of BLQ/ALQ Values	3/0	47/0	
		Vehicles	N	1	64	NA
			MEAN, GEO MEAN	0.057, 0.057	0.006, NA	
			SD, SE	NA, NA	0.0130, 0.0016	
			MEDIAN	0.057	0.000	
			MIN, MAX	0.057, 0.057	0.000, 0.067	
			5%, 95%	NA, NA	0.000, 0.028	
			# of BLQ/ALQ Values	0/0	50/0	
		Other places	N	10	55	0.0076
			MEAN, GEO MEAN	0.016, NA	0.005, NA	
			SD, SE	0.0210, 0.0067	0.0123, 0.0017	
			MEDIAN	0.010	0.000	
			MIN, MAX	0.000, 0.067	0.000, 0.060	
			5%, 95%	0.000, 0.067	0.000, 0.028	
			# of BLQ/ALQ Values	5/0	45/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438313

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 40 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 3	Harrogate Cotinine-N-glucuronide (nmol/mg Creatinine)	Away from home combined	N	15	50	0.0003
			MEAN, GEO MEAN	0.017, NA	0.003, NA	
			SD, SE	0.0210, 0.0054	0.0101, 0.0014	
			MEDIAN	0.011	0.000	
			MIN, MAX	0.000, 0.067	0.000, 0.060	
			5%, 95%	0.000, 0.067	0.000, 0.027	
			# of BLQ/ALQ Values	7/0	43/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438314

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 41 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 6	Harrogate 4-Aminobiphenyl-Hb adduct (pg/g hemoglobin)	Spouse at home	N	2	63	0.0551
			MEAN, GEO MEAN	14.12, 13.91	8.64, 7.82	
			SD, SE	3.373, 2.385	4.510, 0.568	
			MEDIAN	14.12	7.37	
			MIN, MAX	11.73, 16.50	4.09, 27.86	
			5%, 95%	11.73, 16.50	4.36, 15.91	
		Others at home	# of BLQ/ALQ Values	0/0	0/0	NA
			N	1	64	
			MEAN, GEO MEAN	9.65, 9.65	8.80, 7.94	
			SD, SE	NA, NA	4.594, 0.574	
			MEDIAN	9.65	7.44	
			MIN, MAX	9.65, 9.65	4.09, 27.86	
		At home combined	5%, 95%	NA, NA	4.36, 16.50	0.0406
			# of BLQ/ALQ Values	0/0	0/0	
			N	3	62	
			MEAN, GEO MEAN	12.63, 12.32	8.62, 7.79	
			SD, SE	3.512, 2.028	4.545, 0.577	
			MEDIAN	11.73	7.36	
		Work	MIN, MAX	9.65, 16.50	4.09, 27.86	0.9129
			5%, 95%	9.65, 16.50	4.36, 15.91	
			# of BLQ/ALQ Values	0/0	0/0	
			N	3	62	
			MEAN, GEO MEAN	8.01, 7.57	8.85, 7.98	
			SD, SE	3.360, 1.940	4.627, 0.588	
			MEDIAN	7.12	7.52	
			MIN, MAX	5.19, 11.73	4.09, 27.86	
			5%, 95%	5.19, 11.73	4.36, 16.50	
			# of BLQ/ALQ Values	0/0	0/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438315

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-3
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 42 of 42)

Timepoint	Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Week 6	Harrogate 4-Aminobiphenyl-Hb adduct (pg/g hemoglobin)	Vehicles	N	3	62	0.2949
			MEAN, GEO MEAN	9.47, 9.30	8.78, 7.90	
			SD, SE	2.184, 1.261	4.651, 0.591	
			MEDIAN	9.31	7.43	
			MIN, MAX	7.37, 11.73	4.09, 27.86	
			5%, 95%	7.37, 11.73	4.36, 16.50	
			# of BLQ/ALQ Values	0/0	0/0	
		Other places	N	19	46	1.0000
			MEAN, GEO MEAN	9.30, 8.12	8.61, 7.89	
			SD, SE	6.063, 1.391	3.836, 0.566	
			MEDIAN	7.35	7.52	
			MIN, MAX	4.31, 27.86	4.09, 20.64	
			5%, 95%	4.31, 27.86	4.36, 15.91	
			# of BLQ/ALQ Values	0/0	0/0	
		Away from home combined	N	21	44	0.9497
			MEAN, GEO MEAN	9.10, 8.03	8.67, 7.93	
			SD, SE	5.785, 1.262	3.913, 0.590	
			MEDIAN	7.35	7.62	
			MIN, MAX	4.31, 27.86	4.09, 20.64	
			5%, 95%	4.49, 22.67	4.36, 15.91	
			# of BLQ/ALQ Values	0/0	0/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438316

Final Draft: 22 October 2003

Page 347 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-4
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 1 of 16)

Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Harrogate 4-Aminobiphenyl-Hb adduct (pg/g hemoglobin)	Spouse at home	N	2	63	0.1656
		MEAN, GEO MEAN	9.17, 9.15	7.22, 6.44	
		SD, SE	0.856, 0.605	3.755, 0.473	
		MEDIAN	9.17	6.54	
		MIN, MAX	8.56, 9.77	2.49, 23.25	
		5%, 95%	8.56, 9.77	3.12, 13.59	
		# of BLQ/ALQ Values	0/0	0/0	
	Others at home	N	7	58	0.0865
		MEAN, GEO MEAN	8.98, 8.56	7.07, 6.30	
		SD, SE	3.036, 1.147	3.756, 0.493	
		MEDIAN	8.31	6.52	
		MIN, MAX	5.47, 13.87	2.49, 23.25	
		5%, 95%	5.47, 13.87	2.95, 13.59	
		# of BLQ/ALQ Values	0/0	0/0	
	At home combined	N	9	56	0.0250
		MEAN, GEO MEAN	9.02, 8.69	7.00, 6.22	
		SD, SE	2.648, 0.883	3.801, 0.508	
		MEDIAN	8.56	6.37	
		MIN, MAX	5.47, 13.87	2.49, 23.25	
		5%, 95%	5.47, 13.87	2.95, 13.59	
		# of BLQ/ALQ Values	0/0	0/0	
	Work	N	4	61	0.5391
		MEAN, GEO MEAN	8.05, 7.13	7.23, 6.48	
		SD, SE	3.839, 1.920	3.731, 0.478	
		MEDIAN	8.80	6.54	
		MIN, MAX	2.95, 11.63	2.49, 23.25	
		5%, 95%	2.95, 11.63	3.21, 13.59	
		# of BLQ/ALQ Values	0/0	0/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.
Week 1 biomarker data used.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438317

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-4
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 2 of 16)

Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Harrogate 4-Aminobiphenyl-11b adduct (pg/g hemoglobin)	Vehicles	N	4	61	0.1947
		MEAN, GEO MEAN	8.80, 8.48	7.18, 6.40	
		SD, SE	2.600, 1.300	3.768, 0.482	
		MEDIAN	9.04	6.54	
		MIN, MAX	5.47, 11.63	2.49, 23.25	
		5%, 95%	5.47, 11.63	3.12, 13.59	
		# of BLQ/ALQ Values	0/0	0/0	
	Other places	N	21	44	0.4787
		MEAN, GEO MEAN	7.59, 6.86	7.13, 6.35	
		SD, SE	3.461, 0.755	3.857, 0.581	
		MEDIAN	6.95	6.54	
		MIN, MAX	2.95, 13.87	2.49, 23.25	
		5%, 95%	3.94, 13.59	3.12, 12.31	
		# of BLQ/ALQ Values	0/0	0/0	
	Away from home combined	N	25	40	0.2777
		MEAN, GEO MEAN	7.63, 6.98	7.06, 6.24	
		SD, SE	3.239, 0.648	4.004, 0.633	
		MEDIAN	7.34	6.52	
		MIN, MAX	2.95, 13.87	2.49, 23.25	
		5%, 95%	3.94, 13.59	3.01, 14.84	
		# of BLQ/ALQ Values	0/0	0/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

Week 1 biomarker data used.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438318

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-4
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 3 of 16)

Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Harrogate Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0331
		MEAN, GEO MEAN	0.308, 0.275	0.065, NA	
		SD, SE	0.1966, 0.1390	0.1100, 0.0139	
		MEDIAN	0.308	0.033	
		MIN, MAX	0.169, 0.447	0.000, 0.677	
		5%, 95%	0.169, 0.447	0.017, 0.306	
		# of BLQ/ALQ Values	0/0	0/0	
	Others at home	N	7	58	0.0584
		MEAN, GEO MEAN	0.184, 0.087	0.059, NA	
		SD, SE	0.2444, 0.0924	0.0886, 0.0116	
		MEDIAN	0.051	0.033	
		MIN, MAX	0.017, 0.677	0.000, 0.447	
		5%, 95%	0.017, 0.677	0.016, 0.306	
		# of BLQ/ALQ Values	0/0	0/0	
	At home combined	N	9	56	0.0055
		MEAN, GEO MEAN	0.212, 0.112	0.051, NA	
		SD, SE	0.2293, 0.0764	0.0715, 0.0096	
		MEDIAN	0.127	0.033	
		MIN, MAX	0.017, 0.677	0.000, 0.430	
		5%, 95%	0.017, 0.677	0.016, 0.183	
		# of BLQ/ALQ Values	0/0	0/0	
	Work	N	4	61	0.8903
		MEAN, GEO MEAN	0.059, 0.043	0.074, NA	
		SD, SE	0.0534, 0.0267	0.1221, 0.0156	
		MEDIAN	0.041	0.033	
		MIN, MAX	0.016, 0.136	0.000, 0.677	
		5%, 95%	0.016, 0.136	0.017, 0.340	
		# of BLQ/ALQ Values	0/0	0/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.
Week 1 biomarker data used.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438319

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-4
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 4 of 16)

Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Harrogate Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)	Vehicles	N	4	61	0.0120
		MEAN, GEO MEAN	0.222, 0.140	0.063, NA	
		SD, SE	0.2031, 0.1015	0.1069, 0.0137	
		MEDIAN	0.196	0.033	
		MIN, MAX	0.049, 0.447	0.000, 0.677	
		5%, 95%	0.049, 0.447	0.017, 0.183	
		# of BLQ/ALQ Values	0/0	0/0	
	Other places	N	21	44	0.1205
		MEAN, GEO MEAN	0.095, 0.049	0.062, NA	
		SD, SE	0.1326, 0.0289	0.1117, 0.0168	
		MEDIAN	0.043	0.033	
		MIN, MAX	0.005, 0.447	0.000, 0.677	
		5%, 95%	0.017, 0.430	0.017, 0.173	
		# of BLQ/ALQ Values	0/0	0/0	
	Away from home combined	N	25	40	0.0409
		MEAN, GEO MEAN	0.102, 0.053	0.055, NA	
		SD, SE	0.1323, 0.0265	0.1073, 0.0170	
		MEDIAN	0.043	0.033	
		MIN, MAX	0.005, 0.447	0.000, 0.677	
		5%, 95%	0.016, 0.430	0.017, 0.171	
		# of BLQ/ALQ Values	0/0	0/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.
Week 1 biomarker data used.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438320

Final Draft: 22 October 2003

Page 351 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-4
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 5 of 16)

Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Harrogate Nicotine (nmol/rug Creatinine)	Spouse at home	N	2	63	0.0271
		MEAN, GEO MEAN	0.043, 0.041	0.019, NA	
		SD, SE	0.0170, 0.0120	0.0463, 0.0058	
		MEDIAN	0.043	0.006	
		MIN, MAX	0.031, 0.055	0.000, 0.271	
		5%, 95%	0.031, 0.055	0.000, 0.074	
		# of BLQ/ALQ Values	0/0	51/0	
	Others at home	N	7	58	0.0761
		MEAN, GEO MEAN	0.056, 0.021	0.015, NA	
		SD, SE	0.0913, 0.0345	0.0361, 0.0047	
		MEDIAN	0.012	0.006	
		MIN, MAX	0.006, 0.253	0.000, 0.271	
		5%, 95%	0.006, 0.253	0.000, 0.055	
		# of BLQ/ALQ Values	4/0	47/0	
	At home combined	N	9	56	0.0068
		MEAN, GEO MEAN	0.053, 0.025	0.014, NA	
		SD, SE	0.0795, 0.0265	0.0363, 0.0048	
		MEDIAN	0.018	0.006	
		MIN, MAX	0.006, 0.253	0.000, 0.271	
		5%, 95%	0.006, 0.253	0.000, 0.018	
		# of BLQ/ALQ Values	4/0	47/0	
	Work	N	4	61	0.1707
		MEAN, GEO MEAN	0.006, NA	0.021, NA	
		SD, SE	0.0049, 0.0024	0.0472, 0.0060	
		MEDIAN	0.006	0.012	
		MIN, MAX	0.000, 0.012	0.000, 0.271	
		5%, 95%	0.000, 0.012	0.006, 0.074	
		# of BLQ/ALQ Values	3/0	48/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.
Week 1 biomarker data used.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438321

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-4
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 6 of 16)

Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Harrogate Nicotine (nmol/mg Creatinine)	Vehicles	N	4	61	0.0491
		MEAN, GEO MEAN	0.041, 0.027	0.018, NA	
		SD, SE	0.0364, 0.0182	0.0463, 0.0059	
		MEDIAN	0.037	0.006	
		MIN, MAX	0.006, 0.086	0.000, 0.271	
		5%, 95%	0.006, 0.086	0.000, 0.031	
		# of BLQ/ALQ Values	2/0	49/0	
	Other places	N	21	44	0.8106
		MEAN, GEO MEAN	0.026, NA	0.017, NA	
		SD, SE	0.0589, 0.0128	0.0386, 0.0058	
		MEDIAN	0.006	0.012	
		MIN, MAX	0.000, 0.271	0.000, 0.253	
		5%, 95%	0.006, 0.074	0.000, 0.031	
		# of BLQ/ALQ Values	14/0	37/0	
	Away from home combined	N	25	40	0.9254
		MEAN, GEO MEAN	0.026, NA	0.016, NA	
		SD, SE	0.0555, 0.0111	0.0389, 0.0061	
		MEDIAN	0.006	0.012	
		MIN, MAX	0.000, 0.271	0.000, 0.253	
		5%, 95%	0.000, 0.086	0.003, 0.025	
		# of BLQ/ALQ Values	16/0	35/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.
Week 1 biomarker data used.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438322

Final Draft: 22 October 2003

Page 353 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-4
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 7 of 16)

Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Harrogate Cotinine (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0308
		MEAN, GEO MEAN	0.034, 0.032	0.013, NA	
		SD, SE	0.0156, 0.0110	0.0170, 0.0021	
		MEDIAN	0.034	0.006	
		MIN, MAX	0.023, 0.045	0.000, 0.114	
		5%, 95%	0.023, 0.045	0.000, 0.051	
		# of BLQ/ALQ Values	0/0	49/0	
	Others at home	N	7	58	0.0853
		MEAN, GEO MEAN	0.032, 0.017	0.011, NA	
		SD, SE	0.0404, 0.0153	0.0108, 0.0014	
		MEDIAN	0.011	0.006	
		MIN, MAX	0.006, 0.114	0.000, 0.057	
		5%, 95%	0.006, 0.114	0.000, 0.045	
		# of BLQ/ALQ Values	4/0	45/0	
	At home combined	N	9	56	0.0084
		MEAN, GEO MEAN	0.032, 0.020	0.010, NA	
		SD, SE	0.0355, 0.0118	0.0098, 0.0013	
		MEDIAN	0.017	0.006	
		MIN, MAX	0.006, 0.114	0.000, 0.057	
		5%, 95%	0.006, 0.114	0.000, 0.028	
		# of BLQ/ALQ Values	4/0	45/0	
	Work	N	4	61	0.7387
		MEAN, GEO MEAN	0.009, NA	0.014, NA	
		SD, SE	0.0077, 0.0036	0.0177, 0.0023	
		MEDIAN	0.009	0.006	
		MIN, MAX	0.000, 0.017	0.000, 0.114	
		5%, 95%	0.000, 0.017	0.006, 0.051	
		# of BLQ/ALQ Values	3/0	46/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.
Week 1 biomarker data used.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438323

Final Draft: 22 October 2003

Page 354 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-4
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 8 of 16)

Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Harrogate Cotinine (nmol/mg Creatinine)	Vehicles	N	4	61	0.0537
		MEAN, GEO MEAN	0.031, 0.023	0.012, NA	
		SD, SE	0.0238, 0.0119	0.0164, 0.0021	
		MEDIAN	0.031	0.006	
		MIN, MAX	0.006, 0.057	0.000, 0.114	
		5%, 95%	0.006, 0.057	0.000, 0.028	
		# of BLQ/ALQ Values	2/0	47/0	
	Other places	N	21	44	0.4742
		MEAN, GEO MEAN	0.014, NA	0.013, NA	
		SD, SE	0.0161, 0.0035	0.0180, 0.0027	
		MEDIAN	0.006	0.011	
		MIN, MAX	0.000, 0.057	0.000, 0.114	
		5%, 95%	0.006, 0.051	0.000, 0.028	
		# of BLQ/ALQ Values	13/0	36/0	
	Away from home combined	N	25	40	0.9657
		MEAN, GEO MEAN	0.015, NA	0.012, NA	
		SD, SE	0.0173, 0.0035	0.0174, 0.0027	
		MEDIAN	0.006	0.011	
		MIN, MAX	0.000, 0.057	0.000, 0.114	
		5%, 95%	0.000, 0.057	0.003, 0.026	
		# of BLQ/ALQ Values	15/0	34/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.

Week 1 biomarker data used.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438324

Final Draft: 22 October 2003

Page 355 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-4
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 9 of 16)

Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Harrogate Trans-3-hydroxycotinine (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0228
		MEAN, GEO MEAN	0.149, 0.131	0.022, NA	
		SD, SE	0.0997, 0.0705	0.0338, 0.0043	
		MEDIAN	0.149	0.010	
		MIN, MAX	0.078, 0.219	0.000, 0.187	
		5%, 95%	0.078, 0.219	0.005, 0.083	
		# of BLQ/ALQ Values	0/0	22/0	
	Others at home	N	7	58	0.0993
		MEAN, GEO MEAN	0.063, 0.029	0.021, NA	
		SD, SE	0.0785, 0.0297	0.0333, 0.0044	
		MEDIAN	0.016	0.010	
		MIN, MAX	0.005, 0.187	0.000, 0.219	
		5%, 95%	0.005, 0.187	0.005, 0.083	
		# of BLQ/ALQ Values	2/0	20/0	
	At home combined	N	9	56	0.0086
		MEAN, GEO MEAN	0.082, 0.040	0.017, NA	
		SD, SE	0.0854, 0.0285	0.0192, 0.0026	
		MEDIAN	0.042	0.010	
		MIN, MAX	0.005, 0.219	0.000, 0.099	
		5%, 95%	0.005, 0.219	0.005, 0.068	
		# of BLQ/ALQ Values	2/0	20/0	
	Work	N	4	61	0.8557
		MEAN, GEO MEAN	0.023, 0.015	0.026, NA	
		SD, SE	0.0262, 0.0131	0.0428, 0.0055	
		MEDIAN	0.013	0.010	
		MIN, MAX	0.005, 0.062	0.000, 0.219	
		5%, 95%	0.005, 0.062	0.005, 0.099	
		# of BLQ/ALQ Values	1/0	21/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.
Week 1 biomarker data used.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438325

Final Draft: 22 October 2003

Page 356 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-4
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 10 of 16)

Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Harrogate Trans-3-hydroxycotinine (nmol/mg Creatinine)	Vehicles	N	4	61	0.0210
		MEAN, GEO MEAN	0.110, 0.057	0.020, NA	
		SD, SE	0.1088, 0.0544	0.0278, 0.0036	
		MEDIAN	0.102	0.010	
		MIN, MAX	0.016, 0.219	0.000, 0.166	
		5%, 95%	0.016, 0.219	0.005, 0.078	
		# of BLQ/ALQ Values	1/0	21/0	
	Other places	N	21	44	0.0481
		MEAN, GEO MEAN	0.034, 0.018	0.022, NA	
		SD, SE	0.0498, 0.0109	0.0374, 0.0056	
		MEDIAN	0.016	0.010	
		MIN, MAX	0.005, 0.219	0.000, 0.187	
		5%, 95%	0.005, 0.099	0.005, 0.078	
		# of BLQ/ALQ Values	3/0	19/0	
	Away from home combined	N	25	40	0.0126
		MEAN, GEO MEAN	0.039, 0.020	0.017, NA	
		SD, SE	0.0556, 0.0111	0.0277, 0.0044	
		MEDIAN	0.016	0.010	
		MIN, MAX	0.005, 0.219	0.000, 0.166	
		5%, 95%	0.005, 0.187	0.005, 0.060	
		# of BLQ/ALQ Values	4/0	18/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.
Week 1 biomarker data used.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438326

Final Draft: 22 October 2003

Page 357 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-4
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 11 of 16)

Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Harrogate Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)	Spouse at home	N	2	51	0.0198
		MEAN, GEO MEAN	0.039, 0.036	0.005, NA	
		SD, SE	0.0198, 0.0140	0.0090, 0.0013	
		MEDIAN	0.039	0.001	
		MIN, MAX	0.025, 0.053	0.000, 0.051	
		5%, 95%	0.025, 0.053	0.000, 0.018	
		# of BLQ/ALQ Values	0/0	22/0	
	Others at home	N	7	46	0.5163
		MEAN, GEO MEAN	0.010, NA	0.006, NA	
		SD, SE	0.0184, 0.0069	0.0101, 0.0015	
		MEDIAN	0.003	0.001	
		MIN, MAX	0.000, 0.051	0.000, 0.053	
		5%, 95%	0.000, 0.051	0.000, 0.025	
		# of BLQ/ALQ Values	2/0	20/0	
	At home combined	N	9	44	0.0750
		MEAN, GEO MEAN	0.016, NA	0.004, NA	
		SD, SE	0.0216, 0.0072	0.0066, 0.0010	
		MEDIAN	0.005	0.001	
		MIN, MAX	0.000, 0.053	0.000, 0.034	
		5%, 95%	0.000, 0.053	0.000, 0.015	
		# of BLQ/ALQ Values	2/0	20/0	
	Work	N	4	49	0.7419
		MEAN, GEO MEAN	0.005, NA	0.006, NA	
		SD, SE	0.0048, 0.0024	0.0118, 0.0017	
		MEDIAN	0.004	0.002	
		MIN, MAX	0.000, 0.010	0.000, 0.053	
		5%, 95%	0.000, 0.010	0.000, 0.034	
		# of BLQ/ALQ Values	1/0	21/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.
Week 1 biomarker data used.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438327

Final Draft: 22 October 2003

Page 358 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-4
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 12 of 16)

Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Harrogate Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)	Vehicles	N	4	49	0.3232
		MEAN, GEO MEAN	0.016, NA	0.005, NA	
		SD, SE	0.0250, 0.0125	0.0096, 0.0014	
		MEDIAN	0.005	0.001	
		MIN, MAX	0.000, 0.053	0.000, 0.051	
		5%, 95%	0.000, 0.053	0.000, 0.025	
		# of BLQ/ALQ Values	1/0	21/0	
	Other places	N	18	35	0.0016
		MEAN, GEO MEAN	0.010, NA	0.004, NA	
		SD, SE	0.0135, 0.0032	0.0097, 0.0016	
		MEDIAN	0.006	0.000	
		MIN, MAX	0.000, 0.053	0.000, 0.051	
		5%, 95%	0.000, 0.053	0.000, 0.025	
		# of BLQ/ALQ Values	3/0	19/0	
	Away from home combined	N	22	31	0.0021
		MEAN, GEO MEAN	0.009, NA	0.004, NA	
		SD, SE	0.0125, 0.0027	0.0103, 0.0018	
		MEDIAN	0.005	0.000	
		MIN, MAX	0.000, 0.053	0.000, 0.051	
		5%, 95%	0.000, 0.034	0.000, 0.025	
		# of BLQ/ALQ Values	4/0	18/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.
Week 1 biomarker data used.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438328

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-4
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 13 of 16)

Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Harrogate Nicotine-N-glucuronide (nmol/mg Creatinine)	Spouse at home	N	2	60	0.3249
		MEAN, GEO MEAN	0.006, NA	0.002, NA	
		SD, SE	0.0085, 0.0060	0.0047, 0.0006	
		MEDIAN	0.006	0.000	
		MIN, MAX	0.000, 0.012	0.000, 0.023	
		5%, 95%	0.000, 0.012	0.000, 0.013	
		# of BLQ/ALQ Values	0/0	51/0	
	Others at home	N	6	56	0.0164
		MEAN, GEO MEAN	0.006, NA	0.002, NA	
		SD, SE	0.0080, 0.0033	0.0042, 0.0006	
		MEDIAN	0.003	0.000	
		MIN, MAX	0.000, 0.021	0.000, 0.023	
		5%, 95%	0.000, 0.021	0.000, 0.012	
		# of BLQ/ALQ Values	4/0	47/0	
	At home combined	N	8	54	0.0081
		MEAN, GEO MEAN	0.006, NA	0.001, NA	
		SD, SE	0.0075, 0.0026	0.0040, 0.0005	
		MEDIAN	0.003	0.000	
		MIN, MAX	0.000, 0.021	0.000, 0.023	
		5%, 95%	0.000, 0.021	0.000, 0.009	
		# of BLQ/ALQ Values	4/0	47/0	
	Work	N	4	58	0.3144
		MEAN, GEO MEAN	0.002, NA	0.002, NA	
		SD, SE	0.0024, 0.0012	0.0049, 0.0006	
		MEDIAN	0.002	0.000	
		MIN, MAX	0.000, 0.005	0.000, 0.023	
		5%, 95%	0.000, 0.005	0.000, 0.016	
		# of BLQ/ALQ Values	3/0	48/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.
Week 1 biomarker data used.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438329

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-4
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 14 of 16)

Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Harrogate Nicotine-N-glucuronide (nmol/mg Creatinine)	Vehicles	N	3	59	0.1050
		MEAN, GEO MEAN	0.005, NA	0.002, NA	
		SD, SE	0.0062, 0.0036	0.0047, 0.0006	
		MEDIAN	0.003	0.000	
		MIN, MAX	0.000, 0.012	0.000, 0.023	
		5%, 95%	0.000, 0.012	0.000, 0.016	
		# of BLQ/ALQ Values	2/0	49/0	
	Other places	N	20	42	0.0305
		MEAN, GEO MEAN	0.003, NA	0.001, NA	
		SD, SE	0.0057, 0.0013	0.0042, 0.0007	
		MEDIAN	0.000	0.000	
		MIN, MAX	0.000, 0.023	0.000, 0.021	
		5%, 95%	0.000, 0.018	0.000, 0.008	
		# of BLQ/ALQ Values	14/0	37/0	
	Away from home combined	N	23	39	0.0241
		MEAN, GEO MEAN	0.003, NA	0.001, NA	
		SD, SE	0.0054, 0.0011	0.0044, 0.0007	
		MEDIAN	0.000	0.000	
		MIN, MAX	0.000, 0.023	0.000, 0.021	
		5%, 95%	0.000, 0.012	0.000, 0.016	
		# of BLQ/ALQ Values	16/0	35/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.
Week 1 biomarker data used.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438330

Final Draft: 22 October 2003

Page 361 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-4
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 15 of 16)

Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Harrogate Cotinine-N-glucuronide (nmol/mg Creatinine)	Spouse at home	N	2	63	0.0334
		MEAN, GEO MEAN	0.038, 0.026	0.007, NA	
		SD, SE	0.0396, 0.0280	0.0161, 0.0020	
		MEDIAN	0.038	0.000	
		MIN, MAX	0.010, 0.066	0.000, 0.075	
		5%, 95%	0.010, 0.066	0.000, 0.049	
		# of BLQ/ALQ Values	0/0	49/0	
	Others at home	N	7	58	0.0736
		MEAN, GEO MEAN	0.022, NA	0.007, NA	
		SD, SE	0.0292, 0.0110	0.0150, 0.0020	
		MEDIAN	0.009	0.000	
		MIN, MAX	0.000, 0.075	0.000, 0.066	
		5%, 95%	0.000, 0.075	0.000, 0.055	
		# of BLQ/ALQ Values	4/0	45/0	
	At home combined	N	9	56	0.0074
		MEAN, GEO MEAN	0.026, NA	0.006, NA	
		SD, SE	0.0297, 0.0099	0.0130, 0.0017	
		MEDIAN	0.010	0.000	
		MIN, MAX	0.000, 0.075	0.000, 0.064	
		5%, 95%	0.000, 0.075	0.000, 0.036	
		# of BLQ/ALQ Values	4/0	45/0	
	Work	N	4	61	0.3227
		MEAN, GEO MEAN	0.011, NA	0.008, NA	
		SD, SE	0.0169, 0.0084	0.0176, 0.0023	
		MEDIAN	0.004	0.000	
		MIN, MAX	0.000, 0.036	0.000, 0.075	
		5%, 95%	0.000, 0.036	0.000, 0.055	
		# of BLQ/ALQ Values	3/0	46/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.
Week 1 biomarker data used.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438331

Final Draft: 22 October 2003

Page 362 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-4
Comparison Between Non-Smokers Exposed and Non-Smokers Not Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 16 of 16)

Analytical Lab Biomarker	Source of Exposure ^a	Statistic	Exposed	Not-exposed	P-value ^b
Harrogate Cotinine-N-glucuronide (nmol/mg Creatinine)	Vehicles	N	4	61	0.1024
		MEAN, GEO MEAN	0.024, NA	0.007, NA	
		SD, SE	0.0298, 0.0149	0.0162, 0.0021	
		MEDIAN	0.014	0.000	
		MIN, MAX	0.000, 0.066	0.000, 0.075	
		5%, 95%	0.000, 0.066	0.000, 0.049	
		# of BLQ/ALQ Values	2/0	47/0	
	Other places	N	21	44	0.0106
		MEAN, GEO MEAN	0.012, NA	0.006, NA	
		SD, SE	0.0196, 0.0043	0.0162, 0.0024	
		MEDIAN	0.006	0.000	
		MIN, MAX	0.000, 0.066	0.000, 0.075	
		5%, 95%	0.000, 0.064	0.000, 0.049	
		# of BLQ/ALQ Values	13/0	36/0	
	Away from home combined	N	25	40	0.0020
		MEAN, GEO MEAN	0.013, NA	0.006, NA	
		SD, SE	0.0189, 0.0038	0.0161, 0.0025	
		MEDIAN	0.006	0.000	
		MIN, MAX	0.000, 0.066	0.000, 0.075	
		5%, 95%	0.000, 0.064	0.000, 0.052	
		# of BLQ/ALQ Values	15/0	34/0	

NOTE: Source of exposure to environmental tobacco smoke is from at least one of the following: spouse at home, others at home, work, vehicles, other places.
Week 1 biomarker data used.

^a Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^b P-value from Wilcoxon rank-sum test.

PM3006438332

Final Draft: 22 October 2003

Page 363 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-5
Comparison of Duration of Exposure of Non-Smokers Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 1 of 13)

Timepoint	Biomarker	Duration of Exposure ^a	Independent Variable ^b	95% Confidence Interval ^c	Pearson Correlation Coefficient (P-value)	Spearman rank-order Coefficient (P-value)
Week 1	4-Aminobiphenyl-Hb adduct (pg/g hemoglobin)	Non-Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.90, 0.86)	-0.09(0.8830)	0.00(1.0000)
			At home combined	(-0.76, 0.75)	-0.01(0.9909)	0.04(0.9365)
			Work	(-0.99, 0.73)	-0.77(0.2296)	-0.80(0.2000)
			Vehicles	(NA, NA)	1.00(NA)	1.00(NA)
			Other places	(-0.30, 0.54)	0.15(0.5220)	-0.06(0.8118)
			Away from home combined	(-0.33, 0.46)	0.08(0.7167)	-0.12(0.5542)
		Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.90, 0.86)	-0.09(0.8830)	0.00(1.0000)
			At home combined	(-0.74, 0.76)	0.02(0.9633)	0.04(0.9365)
			Work	(-0.98, 0.93)	-0.31(0.6922)	-0.40(0.6000)
			Vehicles	(NA, NA)	1.00(NA)	1.00(NA)
			Other places	(-0.47, 0.39)	-0.04(0.8482)	-0.05(0.8447)
			Away from home combined	(-0.41, 0.38)	-0.02(0.9123)	-0.09(0.6573)
	Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.94, 0.78)	-0.32(0.5948)	0.00(1.0000)
			At home combined	(-0.53, 0.88)	0.37(0.4181)	0.34(0.4601)
			Work	(-1.00, 0.14)	-0.95(0.0513)	-1.00(0.0000)
			Vehicles	(NA, NA)	-1.00(NA)	-1.00(NA)
			Other places	(-0.18, 0.63)	0.28(0.2233)	0.18(0.4361)
			Away from home combined	(-0.19, 0.57)	0.23(0.2792)	0.23(0.2724)
		Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.94, 0.78)	-0.32(0.5948)	0.00(1.0000)
			At home combined	(-0.50, 0.89)	0.40(0.3698)	0.34(0.4601)
			Work	(-1.00, 0.58)	-0.86(0.1376)	-0.80(0.2000)
			Vehicles	(NA, NA)	-1.00(NA)	-1.00(NA)
			Other places	(0.01, 0.73)	0.44(0.0461)	0.20(0.3876)
			Away from home combined	(0.02, 0.69)	0.41(0.0411)	0.22(0.2969)

^a Non-Weighted refers to the number of hours exposed to environmental tobacco smoke. For others at home, spouse at home, and at home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the number of cigarettes smoked. For work, vehicles, other places, and away from home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the intensity (1=mild, 2=moderate, 3=severe) of smoke.

^b Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^c 95% confidence interval for the correlation coefficient.

PM3006438333

Final Draft: 22 October 2003

Page 364 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-5
Comparison of Duration of Exposure of Non-Smokers Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 2 of 13)

Timepoint	Biomarker	Duration of Exposure ^a	Independent Variable ^b	95% Confidence Interval ^c	Pearson Correlation Coefficient (P-value)	Spearman rank-order Coefficient (P-value)
Week 1	Nicotine (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.95, 0.74)	-0.41(0.4952)	-0.30(0.6186)
			At home combined	(-0.77, 0.73)	-0.05(0.9180)	0.25(0.5922)
			Work	(-0.94, 0.98)	0.23(0.7698)	0.21(0.7892)
			Vehicles	(NA, NA)	1.00(NA)	1.00(NA)
			Other places	(0.04, 0.75)	0.47(0.0331)	-0.07(0.7697)
			Away from home combined	(0.02, 0.69)	0.41(0.0421)	0.07(0.7532)
		Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.95, 0.74)	-0.41(0.4952)	-0.30(0.6186)
			At home combined	(-0.75, 0.75)	0.00(0.9940)	0.25(0.5922)
			Work	(-0.78, 0.99)	0.72(0.2788)	0.74(0.2621)
			Vehicles	(NA, NA)	1.00(NA)	1.00(NA)
			Other places	(0.29, 0.84)	0.64(0.0018)	-0.04(0.8624)
			Away from home combined	(0.28, 0.81)	0.61(0.0012)	0.07(0.7294)
	Cotinine (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.95, 0.74)	-0.41(0.4957)	-0.30(0.6186)
			At home combined	(-0.70, 0.80)	0.11(0.8179)	0.25(0.5922)
			Work	(-0.98, 0.94)	-0.22(0.7752)	-0.32(0.6838)
			Vehicles	(NA, NA)	1.00(NA)	1.00(NA)
			Other places	(-0.24, 0.59)	0.22(0.3489)	0.04(0.8746)
			Away from home combined	(-0.25, 0.52)	0.16(0.4463)	-0.04(0.8374)
		Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.95, 0.74)	-0.41(0.4957)	-0.30(0.6186)
			At home combined	(-0.68, 0.81)	0.16(0.7377)	0.25(0.5922)
			Work	(-0.99, 0.88)	-0.51(0.4899)	-0.32(0.6838)
			Vehicles	(NA, NA)	1.00(NA)	1.00(NA)
			Other places	(-0.08, 0.69)	0.37(0.1025)	-0.03(0.8994)
			Away from home combined	(-0.08, 0.64)	0.33(0.1111)	-0.08(0.7045)

^a Non-Weighted refers to the number of hours exposed to environmental tobacco smoke. For others at home, spouse at home, and at home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the number of cigarettes smoked. For work, vehicles, other places, and away from home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the intensity (1=mild, 2=moderate, 3=severe) of smoke.

^b Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^c 95% confidence interval for the correlation coefficient.

PM3006438334

Table 14.1.4.2-5
Comparison of Duration of Exposure of Non-Smokers Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 3 of 13)

Timepoint	Biomarker	Duration of Exposure ^a	Independent Variable ^b	95% Confidence Interval ^c	Pearson Correlation Coefficient (P-value)	Spearman rank-order Coefficient (P-value)
Week 1	Trans-3-hydroxycotinine (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.93, 0.81)	-0.25(0.6802)	0.29(0.6376)
			At home combined	(-0.04, 0.96)	0.73(0.0609)	0.62(0.1395)
			Work	(-1.00, 0.54)	-0.87(0.1258)	-0.80(0.2000)
			Vehicles	(NA, NA)	-1.00(NA)	-1.00(NA)
			Other places	(-0.21, 0.61)	0.24(0.2871)	0.34(0.1261)
			Away from home combined	(-0.24, 0.53)	0.18(0.3990)	0.37(0.0676)
		Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.93, 0.81)	-0.25(0.6802)	0.29(0.6376)
			At home combined	(-0.02, 0.96)	0.75(0.0545)	0.62(0.1395)
			Work	(-1.00, 0.02)	-0.96(0.0405)	-1.00(0.0000)
			Vehicles	(NA, NA)	-1.00(NA)	-1.00(NA)
			Other places	(-0.06, 0.70)	0.39(0.0842)	0.41(0.0618)
			Away from home combined	(-0.07, 0.65)	0.34(0.0984)	0.39(0.0556)
	Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.94, 0.77)	-0.35(0.5629)	0.00(1.0000)
			At home combined	(-0.27, 0.93)	0.61(0.1472)	0.52(0.2274)
			Work	(-1.00, 0.56)	-0.87(0.1323)	-0.40(0.6000)
			Vehicles	(NA, NA)	-1.00(NA)	-1.00(NA)
			Other places	(-0.47, 0.44)	-0.01(0.9517)	0.23(0.3339)
			Away from home combined	(-0.45, 0.37)	-0.05(0.8360)	0.22(0.3070)
		Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.94, 0.77)	-0.35(0.5629)	0.00(1.0000)
			At home combined	(-0.24, 0.94)	0.62(0.1344)	0.52(0.2274)
			Work	(-1.00, 0.62)	-0.84(0.1563)	-0.80(0.2000)
			Vehicles	(NA, NA)	-1.00(NA)	-1.00(NA)
			Other places	(-0.38, 0.52)	0.08(0.7310)	0.38(0.1113)
			Away from home combined	(-0.35, 0.47)	0.07(0.7527)	0.31(0.1458)

^a Non-Weighted refers to the number of hours exposed to environmental tobacco smoke. For others at home, spouse at home, and at home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the number of cigarettes smoked. For work, vehicles, other places, and away from home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the intensity (1=mild, 2=moderate, 3=severe) of smoke.

^b Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^c 95% confidence interval for the correlation coefficient.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-5
Comparison of Duration of Exposure of Non-Smokers Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 4 of 13)

Timepoint	Biomarker	Duration of Exposure ^a	Independent Variable ^b	95% Confidence Interval ^c	Pearson Correlation Coefficient (P-value)	Spearman rank-order Coefficient (P-value)
Week 1	Nicotine-N-glucuronide (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.94, 0.78)	-0.33(0.5908)	-0.29(0.6376)
			At home combined	(-0.63, 0.84)	0.23(0.6177)	-0.14(0.7620)
			Work	(-0.99, 0.75)	-0.76(0.2450)	-0.80(0.2000)
			Vehicles	(NA, NA)	-1.00(NA)	-1.00(NA)
			Other places	(-0.50, 0.38)	-0.07(0.7550)	0.22(0.3524)
			Away from home combined	(-0.42, 0.39)	-0.02(0.9260)	0.32(0.1295)
		Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.94, 0.78)	-0.33(0.5908)	-0.29(0.6376)
			At home combined	(-0.59, 0.86)	0.30(0.5168)	-0.14(0.7620)
			Work	(-0.98, 0.93)	-0.27(0.7295)	-0.40(0.6000)
			Vehicles	(NA, NA)	-1.00(NA)	-1.00(NA)
			Other places	(-0.32, 0.55)	0.15(0.5382)	0.41(0.0755)
			Away from home combined	(-0.20, 0.57)	0.22(0.3078)	0.42(0.0414)
	Cotinine-N-glucuronide (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.89, 0.87)	-0.05(0.9378)	0.00(1.0000)
			At home combined	(-0.45, 0.90)	0.46(0.2997)	0.28(0.5420)
			Work	(-1.00, 0.31)	-0.93(0.0722)	-1.00(0.0000)
			Vehicles	(NA, NA)	-1.00(NA)	-1.00(NA)
			Other places	(-0.49, 0.36)	-0.08(0.7313)	0.39(0.0844)
			Away from home combined	(-0.48, 0.31)	-0.10(0.6330)	0.36(0.0755)
		Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.89, 0.87)	-0.05(0.9378)	0.00(1.0000)
			At home combined	(-0.42, 0.91)	0.49(0.2661)	0.28(0.5420)
			Work	(-0.99, 0.74)	-0.76(0.2378)	-0.80(0.2000)
			Vehicles	(NA, NA)	-1.00(NA)	-1.00(NA)
			Other places	(-0.40, 0.46)	0.03(0.8843)	0.46(0.0355)
			Away from home combined	(-0.37, 0.42)	0.03(0.8896)	0.40(0.0468)

^a Non-Weighted refers to the number of hours exposed to environmental tobacco smoke. For others at home, spouse at home, and at home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the number of cigarettes smoked. For work, vehicles, other places, and away from home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the intensity (1=mild, 2=moderate, 3=severe) of smoke.

^b Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^c 95% confidence interval for the correlation coefficient.

PM3006438336

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-5
Comparison of Duration of Exposure of Non-Smokers Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 5 of 13)

Timepoint	Biomarker	Duration of Exposure ^a	Independent Variable ^b	95% Confidence Interval ^c	Pearson Correlation Coefficient (P-value)	Spearman rank-order Coefficient (P-value)
Week 2	Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	-1.00(NA)	-1.00(NA)
			Others at home	(0.22, 1.00)	0.97(0.0251)	0.95(0.0513)
			At home combined	(-0.29, 0.96)	0.68(0.1371)	0.81(0.0499)
			Work	(NA, NA)	NA(NA)	NA(NA)
			Vehicles	(NA, NA)	0.22(0.8590)	0.00(1.0000)
			Other places	(-0.50, 0.38)	-0.08(0.7417)	0.47(0.0347)
			Away from home combined	(-0.46, 0.36)	-0.07(0.7672)	0.37(0.0807)
		Weighted	Spouse at home	(NA, NA)	-1.00(NA)	-1.00(NA)
			Others at home	(-0.24, 1.00)	0.94(0.0628)	0.95(0.0513)
			At home combined	(-0.76, 0.85)	0.14(0.7972)	0.81(0.0499)
			Work	(NA, NA)	NA(NA)	NA(NA)
			Vehicles	(NA, NA)	0.22(0.8590)	0.00(1.0000)
			Other places	(-0.47, 0.41)	-0.04(0.8798)	0.38(0.0939)
			Away from home combined	(-0.43, 0.40)	-0.02(0.9269)	0.22(0.3188)
	Nicotine (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	-1.00(NA)	-1.00(NA)
			Others at home	(-0.88, 0.99)	0.51(0.4863)	0.39(0.6111)
			At home combined	(-0.74, 0.87)	0.19(0.7242)	0.19(0.7215)
			Work	(NA, NA)	NA(NA)	NA(NA)
			Vehicles	(NA, NA)	-0.99(0.0965)	-0.87(0.3333)
			Other places	(-0.59, 0.26)	-0.21(0.3836)	-0.01(0.9562)
			Away from home combined	(-0.55, 0.25)	-0.18(0.4047)	0.01(0.9669)
		Weighted	Spouse at home	(NA, NA)	-1.00(NA)	-1.00(NA)
			Others at home	(-0.88, 0.99)	0.52(0.4780)	0.39(0.6111)
			At home combined	(-0.87, 0.74)	-0.18(0.7289)	0.19(0.7215)
			Work	(NA, NA)	NA(NA)	NA(NA)
			Vehicles	(NA, NA)	-0.99(0.0965)	-0.87(0.3333)
			Other places	(-0.57, 0.29)	-0.18(0.4605)	0.03(0.9120)
			Away from home combined	(-0.53, 0.28)	-0.15(0.5019)	0.01(0.9670)

^a Non-Weighted refers to the number of hours exposed to environmental tobacco smoke. For others at home, spouse at home, and at home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the number of cigarettes smoked. For work, vehicles, other places, and away from home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the intensity (1=mild, 2=moderate, 3=severe) of smoke.

^b Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^c 95% confidence interval for the correlation coefficient.

Table 14.1.4.2-5
Comparison of Duration of Exposure of Non-Smokers Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 6 of 13)

Timepoint	Biomarker	Duration of Exposure ^a	Independent Variable ^b	95% Confidence Interval ^c	Pearson Correlation Coefficient (P-value)	Spearman rank-order Coefficient (P-value)
Week 2	Cotinine (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	-1.00(NA)	-1.00(NA)
			Others at home	(-0.25, 1.00)	0.94(0.0642)	0.63(0.3675)
			At home combined	(-0.38, 0.95)	0.62(0.1871)	0.71(0.1170)
			Work	(NA, NA)	NA(NA)	NA(NA)
			Vehicles	(NA, NA)	0.00(1.0000)	0.00(1.0000)
			Other places	(-0.54, 0.33)	-0.13(0.5877)	0.31(0.1854)
			Away from home combined	(-0.50, 0.32)	-0.11(0.6171)	0.29(0.1782)
		Weighted	Spouse at home	(NA, NA)	1.00(NA)	-1.00(NA)
			Others at home	(-0.09, 1.00)	0.95(0.0467)	0.63(0.3675)
			At home combined	(-0.74, 0.86)	0.17(0.7441)	0.71(0.1170)
			Work	(NA, NA)	NA(NA)	NA(NA)
			Vehicles	(NA, NA)	0.00(1.0000)	0.00(1.0000)
			Other places	(-0.51, 0.37)	-0.09(0.7138)	0.26(0.2608)
			Away from home combined	(-0.47, 0.36)	-0.07(0.7660)	0.22(0.3189)
	Trans-3-hydroxycotinine (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	-1.00(NA)	-1.00(NA)
			Others at home	(0.75, 1.00)	0.99(0.0056)	0.95(0.0513)
			At home combined	(-0.21, 0.97)	0.73(0.1026)	0.79(0.0592)
			Work	(NA, NA)	NA(NA)	NA(NA)
			Vehicles	(NA, NA)	0.50(0.6667)	0.50(0.6667)
			Other places	(-0.05, 0.71)	0.40(0.0826)	0.45(0.0440)
			Away from home combined	(-0.04, 0.69)	0.38(0.0718)	0.33(0.1216)
		Weighted	Spouse at home	(NA, NA)	-1.00(NA)	-1.00(NA)
			Others at home	(0.42, 1.00)	0.98(0.0161)	0.95(0.0513)
			At home combined	(-0.67, 0.89)	0.30(0.5607)	0.79(0.0592)
			Work	(NA, NA)	NA(NA)	NA(NA)
			Vehicles	(NA, NA)	0.50(0.6667)	0.50(0.6667)
			Other places	(0.04, 0.76)	0.47(0.0350)	0.42(0.0678)
			Away from home combined	(0.05, 0.73)	0.45(0.0293)	0.22(0.3034)

^a Non-Weighted refers to the number of hours exposed to environmental tobacco smoke. For others at home, spouse at home, and at home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the number of cigarettes smoked. For work, vehicles, other places, and away from home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the intensity (1=mild, 2=moderate, 3=severe) of smoke.

^b Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^c 95% confidence interval for the correlation coefficient.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-5
Comparison of Duration of Exposure of Non-Smokers Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 7 of 13)

Timepoint	Biomarker	Duration of Exposure ^a	Independent Variable ^b	95% Confidence Interval ^c	Pearson Correlation Coefficient (P-value)	Spearman rank-order Coefficient (P-value)
Week 2	Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	NA(NA)	NA(NA)
			Others at home	(0.95, 1.00)	1.00(0.0009)	0.95(0.0513)
			At home combined	(-0.15, 0.99)	0.84(0.0725)	0.97(0.0048)
			Work	(NA, NA)	NA(NA)	NA(NA)
			Vehicles	(NA, NA)	0.51(0.6562)	0.87(0.3333)
			Other places	(-0.11, 0.72)	0.38(0.1237)	0.23(0.3621)
			Away from home combined	(-0.15, 0.65)	0.30(0.1839)	0.12(0.5940)
		Weighted	Spouse at home	(NA, NA)	NA(NA)	NA(NA)
			Others at home	(0.55, 1.00)	0.99(0.0115)	0.95(0.0513)
			At home combined	(-0.28, 0.99)	0.80(0.1031)	0.97(0.0048)
			Work	(NA, NA)	NA(NA)	NA(NA)
			Vehicles	(NA, NA)	0.51(0.6562)	0.87(0.3333)
			Other places	(-0.02, 0.76)	0.45(0.0579)	0.22(0.3851)
			Away from home combined	(-0.07, 0.69)	0.37(0.0999)	0.03(0.9119)
	Nicotine-N-glucuronide (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.96, 0.96)	0.03(0.9730)	0.78(0.2222)
			At home combined	(-0.81, 0.81)	0.00(0.9971)	0.63(0.1828)
			Work	(NA, NA)	NA(NA)	NA(NA)
			Vehicles	(NA, NA)	NA(NA)	NA(NA)
			Other places	(-0.61, 0.30)	-0.20(0.4285)	0.22(0.3884)
			Away from home combined	(-0.56, 0.28)	-0.17(0.4597)	0.19(0.3995)
		Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.97, 0.95)	-0.13(0.8749)	0.78(0.2222)
			At home combined	(-0.82, 0.80)	-0.03(0.9523)	0.63(0.1828)
			Work	(NA, NA)	NA(NA)	NA(NA)
			Vehicles	(NA, NA)	NA(NA)	NA(NA)
			Other places	(-0.59, 0.33)	-0.17(0.5106)	0.20(0.4188)
			Away from home combined	(-0.54, 0.32)	-0.13(0.5610)	0.10(0.6706)

^a Non-Weighted refers to the number of hours exposed to environmental tobacco smoke. For others at home, spouse at home, and at home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the number of cigarettes smoked. For work, vehicles, other places, and away from home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the intensity (1=mild, 2=moderate, 3=severe) of smoke.

^b Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^c 95% confidence interval for the correlation coefficient.

PM3006438339

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-5
Comparison of Duration of Exposure of Non-Smokers Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 8 of 13)

Timepoint	Biomarker	Duration of Exposure ^a	Independent Variable ^b	95% Confidence Interval ^c	Pearson Correlation Coefficient (P-value)	Spearman rank-order Coefficient (P-value)
Week 2	Cotinine-N-glucuronide (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA , NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.72 , 1.00)	0.78(0.2181)	0.95(0.0513)
			At home combined	(-0.51 , 0.94)	0.52(0.2951)	0.70(0.1248)
			Work	(NA , NA)	NA(NA)	NA(NA)
			Vehicles	(NA , NA)	0.32(0.7946)	0.00(1.0000)
			Other places	(-0.46 , 0.42)	-0.02(0.9219)	0.54(0.0138)
			Away from home combined	(-0.43 , 0.39)	-0.03(0.9083)	0.44(0.0342)
		Weighted	Spouse at home	(NA , NA)	1.00(NA)	1.00(NA)
			Others at home	(-0.81 , 0.99)	0.68(0.3219)	0.95(0.0513)
			At home combined	(-0.82 , 0.81)	-0.02(0.9755)	0.70(0.1248)
			Work	(NA , NA)	NA(NA)	NA(NA)
			Vehicles	(NA , NA)	0.32(0.7946)	0.00(1.0000)
			Other places	(-0.45 , 0.43)	-0.01(0.9666)	0.48(0.0337)
			Away from home combined	(-0.42 , 0.40)	-0.01(0.9648)	0.31(0.1520)

^a Non-Weighted refers to the number of hours exposed to environmental tobacco smoke. For others at home, spouse at home, and at home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the number of cigarettes smoked. For work, vehicles, other places, and away from home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the intensity(1=mild, 2=moderate, 3=severe) of smoke.

^b Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^c 95% confidence interval for the correlation coefficient.

PM3006438340

Final Draft: 22 October 2003

Page 371 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-5
Comparison of Duration of Exposure of Non-Smokers Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 9 of 13)

Timepoint	Biomarker	Duration of Exposure ^a	Independent Variable ^b	95% Confidence Interval ^c	Pearson Correlation Coefficient (P-value)	Spearman rank-order Coefficient (P-value)
Week 3	Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(NA, NA)	NA(NA)	NA(NA)
			At home combined	(NA, NA)	0.98(0.1236)	1.00(0.0000)
			Work	(-0.60, 0.97)	0.60(0.2812)	0.37(0.5418)
			Vehicles	(NA, NA)	NA(NA)	NA(NA)
			Other places	(-0.28, 0.83)	0.42(0.2247)	0.56(0.0910)
			Away from home combined	(0.35, 0.91)	0.73(0.0019)	0.57(0.0261)
		Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(NA, NA)	NA(NA)	NA(NA)
			At home combined	(NA, NA)	0.98(0.1296)	0.50(0.6667)
			Work	(-0.51, 0.98)	0.68(0.2076)	0.54(0.3467)
			Vehicles	(NA, NA)	NA(NA)	NA(NA)
			Other places	(-0.48, 0.75)	0.22(0.5457)	0.53(0.1133)
			Away from home combined	(0.55, 0.94)	0.83(0.0001)	0.63(0.0111)
	Nicotine (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(NA, NA)	NA(NA)	NA(NA)
			At home combined	(NA, NA)	0.99(0.0906)	1.00(0.0000)
			Work	(-0.90, 0.86)	-0.08(0.8999)	-0.57(0.3120)
			Vehicles	(NA, NA)	NA(NA)	NA(NA)
			Other places	(-0.67, 0.58)	-0.07(0.8410)	-0.09(0.8008)
			Away from home combined	(0.25, 0.88)	0.68(0.0056)	-0.02(0.9408)
		Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
			Others at home	(NA, NA)	NA(NA)	NA(NA)
			At home combined	(NA, NA)	0.99(0.0966)	0.50(0.6667)
			Work	(-0.90, 0.87)	-0.07(0.9160)	-0.47(0.4228)
			Vehicles	(NA, NA)	NA(NA)	NA(NA)
			Other places	(-0.82, 0.33)	-0.38(0.2747)	-0.44(0.2061)
			Away from home combined	(0.49, 0.93)	0.80(0.0003)	-0.05(0.8500)

^a Non-Weighted refers to the number of hours exposed to environmental tobacco smoke. For others at home, spouse at home, and at home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the number of cigarettes smoked. For work, vehicles, other places, and away from home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the intensity (1=mild, 2=moderate, 3=severe) of smoke.

^b Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^c 95% confidence interval for the correlation coefficient.

PM3006438341

Final Draft: 22 October 2003

Page 372 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-5
Comparison of Duration of Exposure of Non-Smokers Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 10 of 13)

Timepoint	Biomarker	Duration of Exposure ^a	Independent Variable ^b	95% Confidence Interval ^c	Pearson Correlation Coefficient (P-value)	Spearman rank-order Coefficient (P-value)
Week 3	Cotinine (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA , NA)	1.00(NA)	1.00(NA)
			Others at home	(NA , NA)	NA(NA)	NA(NA)
			At home combined	(NA , NA)	0.97(0.1485)	1.00(0.0000)
			Work	(-0.90 , 0.87)	-0.06(0.9197)	-0.29(0.6366)
			Vehicles	(NA , NA)	NA(NA)	NA(NA)
			Other places	(-0.47 , 0.75)	0.22(0.5343)	0.25(0.4824)
			Away from home combined	(0.18 , 0.87)	0.64(0.0109)	0.29(0.2874)
		Weighted	Spouse at home	(NA , NA)	1.00(NA)	1.00(NA)
			Others at home	(NA , NA)	NA(NA)	NA(NA)
			At home combined	(NA , NA)	0.97(0.1545)	0.50(0.6667)
			Work	(-0.88 , 0.88)	0.01(0.9874)	-0.11(0.8626)
			Vehicles	(NA , NA)	NA(NA)	NA(NA)
			Other places	(-0.57 , 0.68)	0.09(0.8062)	0.30(0.3960)
			Away from home combined	(0.41 , 0.92)	0.76(0.0009)	0.38(0.1661)
	Trans-3-hydroxycotinine (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA , NA)	1.00(NA)	1.00(NA)
			Others at home	(NA , NA)	NA(NA)	NA(NA)
			At home combined	(NA , NA)	0.95(0.2051)	1.00(0.0000)
			Work	(-0.50 , 0.98)	0.68(0.2036)	0.21(0.7406)
			Vehicles	(NA , NA)	NA(NA)	NA(NA)
			Other places	(-0.19 , 0.86)	0.50(0.1392)	0.61(0.0598)
			Away from home combined	(0.36 , 0.91)	0.74(0.0017)	0.62(0.0140)
		Weighted	Spouse at home	(NA , NA)	1.00(NA)	1.00(NA)
			Others at home	(NA , NA)	NA(NA)	NA(NA)
			At home combined	(NA , NA)	0.95(0.2111)	0.50(0.6667)
			Work	(-0.50 , 0.98)	0.68(0.2030)	0.32(0.6042)
			Vehicles	(NA , NA)	NA(NA)	NA(NA)
			Other places	(-0.41 , 0.78)	0.30(0.3982)	0.44(0.2036)
			Away from home combined	(0.58 , 0.95)	0.84(0.0001)	0.62(0.0145)

^a Non-Weighted refers to the number of hours exposed to environmental tobacco smoke. For others at home, spouse at home, and at home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the number of cigarettes smoked. For work, vehicles, other places, and away from home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the intensity (1=mild, 2=moderate, 3=severe) of smoke.

^b Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^c 95% confidence interval for the correlation coefficient.

PM3006438342

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-5
Comparison of Duration of Exposure of Non-Smokers Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 11 of 13)

Timepoint	Biomarker	Duration of Exposure ^a	Independent Variable ^b	95% Confidence Interval ^c	Pearson Correlation Coefficient (P-value)	Spearman rank-order Coefficient (P-value)
Week 3	Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA , NA)	1.00(NA)	1.00(NA)
			Others at home	(NA , NA)	NA(NA)	NA(NA)
			At home combined	(NA , NA)	0.99(0.1048)	1.00(0.0000)
			Work	(0.62 , 1.00)	0.99(0.0094)	0.80(0.2000)
			Vehicles	(NA , NA)	NA(NA)	NA(NA)
			Other places	(0.28 , 0.95)	0.79(0.0105)	0.89(0.0015)
			Away from home combined	(0.38 , 0.93)	0.77(0.0021)	0.93(0.0000)
		Weighted	Spouse at home	(NA , NA)	1.00(NA)	1.00(NA)
			Others at home	(NA , NA)	NA(NA)	NA(NA)
			At home combined	(NA , NA)	0.98(0.1108)	0.50(0.6667)
			Work	(0.17 , 1.00)	0.97(0.0279)	0.63(0.3675)
			Vehicles	(NA , NA)	NA(NA)	NA(NA)
			Other places	(-0.38 , 0.83)	0.38(0.3097)	0.50(0.1747)
			Away from home combined	(0.42 , 0.93)	0.79(0.0014)	0.81(0.0009)
	Nicotine-N-glucuronide (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA , NA)	1.00(NA)	1.00(NA)
			Others at home	(NA , NA)	NA(NA)	NA(NA)
			At home combined	(NA , NA)	0.99(0.0670)	0.50(0.6667)
			Work	(-0.95 , 0.73)	-0.42(0.4794)	-0.34(0.5707)
			Vehicles	(NA , NA)	NA(NA)	NA(NA)
			Other places	(-0.17 , 0.86)	0.52(0.1274)	0.52(0.1232)
			Away from home combined	(0.05 , 0.83)	0.55(0.0342)	0.24(0.3834)
		Weighted	Spouse at home	(NA , NA)	1.00(NA)	1.00(NA)
			Others at home	(NA , NA)	NA(NA)	NA(NA)
			At home combined	(NA , NA)	1.00(0.0610)	1.00(0.0000)
			Work	(-0.94 , 0.79)	-0.31(0.6119)	-0.18(0.7761)
			Vehicles	(NA , NA)	NA(NA)	NA(NA)
			Other places	(-0.08 , 0.89)	0.58(0.0807)	0.56(0.0945)
			Away from home combined	(0.35 , 0.90)	0.73(0.0020)	0.28(0.3122)

^a Non-Weighted refers to the number of hours exposed to environmental tobacco smoke. For others at home, spouse at home, and at home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the number of cigarettes smoked. For work, vehicles, other places, and away from home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the intensity (1=mild, 2=moderate, 3=severe) of smoke.

^b Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^c 95% confidence interval for the correlation coefficient.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-5
Comparison of Duration of Exposure of Non-Smokers Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 12 of 13)

Timepoint	Biomarker	Duration of Exposure ^a	Independent Variable ^b	95% Confidence Interval ^c	Pearson Correlation Coefficient (P-value)	Spearman rank-order Coefficient (P-value)
Week 3	Cotinine-N-glucuronide (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA , NA)	1.00(NA)	1.00(NA)
			Others at home	(NA , NA)	NA(NA)	NA(NA)
			At home combined	(NA , NA)	0.93(0.2384)	0.50(0.6667)
			Work	(-0.38 , 0.98)	0.75(0.1403)	0.62(0.2690)
			Vehicles	(NA , NA)	NA(NA)	NA(NA)
			Other places	(-0.36 , 0.80)	0.35(0.3161)	0.56(0.0905)
			Away from home combined	(0.18 , 0.87)	0.64(0.0109)	0.60(0.0180)
		Weighted	Spouse at home	(NA , NA)	1.00(NA)	1.00(NA)
			Others at home	(NA , NA)	NA(NA)	NA(NA)
			At home combined	(NA , NA)	0.93(0.2324)	1.00(0.0000)
			Work	(-0.22 , 0.99)	0.82(0.0877)	0.74(0.1546)
			Vehicles	(NA , NA)	NA(NA)	NA(NA)
			Other places	(-0.58 , 0.68)	0.08(0.8278)	0.44(0.2036)
			Away from home combined	(0.14 , 0.85)	0.61(0.0158)	0.60(0.0173)

^a Non-Weighted refers to the number of hours exposed to environmental tobacco smoke. For others at home, spouse at home, and at home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the number of cigarettes smoked. For work, vehicles, other places, and away from home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the intensity (1=mild, 2=moderate, 3=severe) of smoke.

^b Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^c 95% confidence interval for the correlation coefficient.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-5
Comparison of Duration of Exposure of Non-Smokers Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Day Period Before Sample Collection
(Page 13 of 13)

Timepoint	Biomarker	Duration of Exposure ^a	Independent Variable ^b	95% Confidence Interval ^c	Pearson Correlation Coefficient (P-value)	Spearman rank-order Coefficient (P-value)
Week 6	4-Aminobiphenyl-Hb adduct (pg/g hemoglobin)	Non-Weighted	Spouse at home	(NA, NA)	-1.00(NA)	-1.00(NA)
			Others at home	(NA, NA)	NA(NA)	NA(NA)
			At home combined	(NA, NA)	-0.18(0.8837)	0.50(0.6667)
			Work	(NA, NA)	0.82(0.3900)	1.00(0.0000)
			Vehicles	(NA, NA)	0.55(0.6263)	0.50(0.6667)
			Other places	(-0.62, 0.25)	-0.23(0.3532)	-0.23(0.3464)
			Away from home combined	(-0.52, 0.34)	-0.11(0.6312)	-0.17(0.4542)
		Weighted	Spouse at home	(NA, NA)	-1.00(NA)	-1.00(NA)
			Others at home	(NA, NA)	NA(NA)	NA(NA)
			At home combined	(NA, NA)	-0.22(0.8618)	0.50(0.6667)
			Work	(NA, NA)	0.52(0.6555)	0.50(0.6667)
			Vehicles	(NA, NA)	0.80(0.4140)	0.50(0.6667)
			Other places	(-0.60, 0.28)	-0.20(0.4090)	-0.14(0.5692)
			Away from home combined	(-0.48, 0.38)	-0.07(0.7762)	-0.11(0.6489)

^a Non-Weighted refers to the number of hours exposed to environmental tobacco smoke. For others at home, spouse at home, and at home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the number of cigarettes smoked. For work, vehicles, other places, and away from home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the intensity (1=mild, 2=moderate, 3=severe) of smoke.

^b Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^c 95% confidence interval for the correlation coefficient.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-6
Comparison of Duration of Exposure of Non-Smokers Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 1 of 4)

Biomarker	Duration of Exposure ^a	Independent Variable ^b	95% Confidence Interval ^c	Pearson Correlation Coefficient (P-value)	Spearman rank-order Coefficient (P-value)
4-Aminobiphenyl-Hb adduct (pg/g hemoglobin)	Non-Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
		Others at home	(-0.83, 0.64)	-0.21(0.6464)	0.21(0.6445)
		At home combined	(-0.71, 0.61)	-0.09(0.8150)	0.17(0.6682)
		Work	(-0.96, 0.96)	0.02(0.9847)	0.00(1.0000)
		Vehicles	(-0.94, 0.98)	0.25(0.7478)	0.32(0.6838)
		Other places	(-0.33, 0.52)	0.11(0.6232)	-0.03(0.9086)
		Away from home combined	(-0.29, 0.49)	0.12(0.5643)	-0.04(0.8463)
	Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
		Others at home	(-0.83, 0.64)	-0.22(0.6397)	0.21(0.6445)
		At home combined	(-0.63, 0.70)	0.06(0.8807)	0.18(0.6368)
		Work	(-0.96, 0.96)	-0.04(0.9624)	0.00(1.0000)
		Vehicles	(-0.94, 0.98)	0.22(0.7781)	0.00(1.0000)
		Other places	(-0.42, 0.44)	0.01(0.9502)	-0.04(0.8531)
		Away from home combined	(-0.33, 0.46)	0.07(0.7234)	-0.08(0.7086)
Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
		Others at home	(-0.63, 0.84)	0.24(0.6093)	0.21(0.6445)
		At home combined	(-0.35, 0.84)	0.41(0.2708)	0.45(0.2242)
		Work	(-1.00, 0.62)	-0.84(0.1560)	-0.80(0.2000)
		Vehicles	(-0.80, 0.99)	0.70(0.3042)	0.32(0.6838)
		Other places	(-0.09, 0.68)	0.35(0.1146)	0.35(0.1230)
		Away from home combined	(-0.31, 0.47)	0.10(0.6495)	0.04(0.8403)
	Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
		Others at home	(-0.53, 0.88)	0.37(0.4161)	0.21(0.6445)
		At home combined	(-0.31, 0.86)	0.45(0.2267)	0.50(0.1705)
		Work	(-1.00, 0.72)	-0.78(0.2162)	-0.80(0.2000)
		Vehicles	(-0.79, 0.99)	0.72(0.2848)	0.40(0.6000)
		Other places	(-0.06, 0.70)	0.38(0.0906)	0.25(0.2823)
		Away from home combined	(-0.33, 0.45)	0.07(0.7380)	-0.01(0.9576)

^a Non-Weighted refers to the number of hours exposed to environmental tobacco smoke. For others at home, spouse at home, and at home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the number of cigarettes smoked. For work, vehicles, other places, and away from home combined, weighted refers to the number of hours exposed to environmental tobacco smoke times the intensity (1=mild, 2=moderate, 3=severe) of smoke.

^b Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^c 95% confidence interval for the correlation coefficient.

PM3006438346

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-6
Comparison of Duration of Exposure of Non-Smokers Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 2 of 4)

Biomarker	Duration of Exposure ^a	Independent Variable ^b	95% Confidence Interval ^c	Pearson Correlation Coefficient (P-value)	Spearman rank-order Coefficient (P-value)
Nicotine (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
		Others at home	(-0.69, 0.80)	0.13(0.7878)	0.16(0.7259)
		At home combined	(-0.62, 0.71)	0.08(0.8377)	0.40(0.2817)
		Work	(-0.99, 0.86)	-0.58(0.4159)	-0.63(0.3675)
		Vehicles	(-0.94, 0.97)	0.19(0.8088)	-0.32(0.6838)
		Other places	(0.02, 0.74)	0.44(0.0435)	0.49(0.0245)
		Away from home combined	(-0.37, 0.42)	0.03(0.8682)	0.18(0.3994)
	Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
		Others at home	(-0.61, 0.85)	0.26(0.5707)	0.16(0.7259)
		At home combined	(-0.63, 0.70)	0.06(0.8707)	0.45(0.2198)
		Work	(-0.99, 0.78)	-0.72(0.2825)	-0.63(0.3675)
		Vehicles	(-0.94, 0.98)	0.22(0.7780)	-0.20(0.8000)
		Other places	(0.26, 0.83)	0.62(0.0028)	0.31(0.1673)
		Away from home combined	(-0.36, 0.43)	0.04(0.8461)	0.13(0.5397)
Cotinine (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
		Others at home	(-0.63, 0.84)	0.23(0.6204)	0.16(0.7259)
		At home combined	(-0.50, 0.78)	0.24(0.5301)	0.40(0.2817)
		Work	(-1.00, -0.74)	-0.99(0.0060)	-1.00(0.0000)
		Vehicles	(-0.92, 0.98)	0.33(0.6715)	-0.32(0.6838)
		Other places	(-0.13, 0.66)	0.32(0.1517)	0.38(0.0871)
		Away from home combined	(-0.41, 0.38)	-0.02(0.9182)	0.00(0.9907)
	Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
		Others at home	(-0.54, 0.88)	0.36(0.4253)	0.16(0.7259)
		At home combined	(-0.53, 0.77)	0.21(0.5913)	0.45(0.2198)
		Work	(-1.00, -0.44)	-0.98(0.0153)	-1.00(0.0000)
		Vehicles	(-0.92, 0.98)	0.36(0.6405)	-0.20(0.8000)
		Other places	(-0.02, 0.72)	0.41(0.0623)	0.25(0.2732)
		Away from home combined	(-0.42, 0.37)	-0.03(0.8803)	-0.02(0.9094)

^a Non-Weighted refers to the number of hours exposed to environmental tobacco smoke. For others at home, spouse at home, and at home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the number of cigarettes smoked. For work, vehicles, other places, and away from home combined, weighted refers to the number of hours exposed to environmental tobacco smoke times the intensity (1=mild, 2=moderate, 3=severe) of smoke.

^b Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^c 95% confidence interval for the correlation coefficient.

PM3006438347

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-6
Comparison of Duration of Exposure of Non-Smokers Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 3 of 4)

Biomarker	Duration of Exposure ^a	Independent Variable ^b	95% Confidence Interval ^c	Pearson Correlation Coefficient (P-value)	Spearman rank-order Coefficient (P-value)
Trans-3-hydroxycotinine (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
		Others at home	(-0.26, 0.93)	0.61(0.1431)	0.45(0.3104)
		At home combined	(0.21, 0.95)	0.77(0.0161)	0.67(0.0486)
		Work	(-1.00, 0.64)	-0.83(0.1680)	-0.80(0.2000)
		Vehicles	(-0.84, 0.99)	0.62(0.3766)	0.33(0.6667)
		Other places	(-0.26, 0.58)	0.19(0.4020)	0.20(0.3908)
		Away from home combined	(-0.33, 0.46)	0.08(0.7059)	-0.06(0.7915)
	Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
		Others at home	(-0.09, 0.95)	0.71(0.0743)	0.45(0.3104)
		At home combined	(0.08, 0.93)	0.71(0.0332)	0.69(0.0412)
		Work	(-0.99, 0.76)	-0.75(0.2504)	-0.80(0.2000)
		Vehicles	(-0.83, 0.99)	0.64(0.3555)	0.32(0.6838)
		Other places	(-0.32, 0.54)	0.13(0.5607)	0.11(0.6399)
		Away from home combined	(-0.35, 0.44)	0.05(0.7990)	-0.10(0.6332)
Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
		Others at home	(-0.81, 0.68)	-0.15(0.7546)	0.25(0.5852)
		At home combined	(-0.38, 0.83)	0.38(0.3094)	0.49(0.1854)
		Work	(-0.99, 0.88)	-0.53(0.4744)	-0.40(0.6000)
		Vehicles	(0.66, 1.00)	0.99(0.0080)	0.63(0.3675)
		Other places	(-0.31, 0.60)	0.18(0.4725)	0.27(0.2871)
		Away from home combined	(-0.25, 0.57)	0.20(0.3826)	0.12(0.6054)
	Weighted	Spouse at home	(NA, NA)	1.00(NA)	1.00(NA)
		Others at home	(-0.76, 0.75)	-0.01(0.9803)	0.25(0.5852)
		At home combined	(-0.08, 0.91)	0.62(0.0755)	0.50(0.1684)
		Work	(-0.99, 0.87)	-0.55(0.4508)	-0.40(0.6000)
		Vehicles	(0.57, 1.00)	0.99(0.0108)	0.40(0.6000)
		Other places	(-0.45, 0.49)	0.02(0.9260)	0.19(0.4480)
		Away from home combined	(-0.32, 0.51)	0.12(0.6006)	0.04(0.8626)

^a Non-Weighted refers to the number of hours exposed to environmental tobacco smoke. For others at home, spouse at home, and at home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the number of cigarettes smoked. For work, vehicles, other places, and away from home combined, weighted refers to the number of hours exposed to environmental tobacco smoke times the intensity (1=mild, 2=moderate, 3=severe) of smoke.

^b Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^c 95% confidence interval for the correlation coefficient.

PM3006438348

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.4.2-6
Comparison of Duration of Exposure of Non-Smokers Exposed to Environmental Tobacco Smoke by Source of Exposure Within 3-Month Period Before Sample Collection at Enrollment
(Page 4 of 4)

Biomarker	Duration of Exposure ^a	Independent Variable ^b	95% Confidence Interval ^c	Pearson Correlation Coefficient (P-value)	Spearman rank-order Coefficient (P-value)
Nicotine-N-glucuronide (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA , NA)	1.00(NA)	1.00(NA)
		Others at home	(-0.86 , 0.75)	-0.15(0.7754)	0.12(0.8268)
		At home combined	(-0.62 , 0.77)	0.15(0.7204)	0.15(0.7294)
		Work	(-0.99 , 0.84)	-0.62(0.3785)	-0.63(0.3675)
		Vehicles	(NA , NA)	0.97(0.1544)	0.87(0.3333)
		Other places	(-0.28 , 0.58)	0.19(0.4266)	0.20(0.3960)
		Away from home combined	(-0.35 , 0.47)	0.08(0.7303)	0.12(0.5948)
	Weighted	Spouse at home	(NA , NA)	1.00(NA)	1.00(NA)
		Others at home	(-0.77 , 0.85)	0.12(0.8200)	0.12(0.8268)
		At home combined	(-0.49 , 0.84)	0.33(0.4194)	0.29(0.4816)
		Work	(-0.99 , 0.84)	-0.64(0.3628)	-0.63(0.3675)
		Vehicles	(NA , NA)	0.96(0.1752)	0.50(0.6667)
		Other places	(-0.27 , 0.59)	0.20(0.3989)	0.25(0.2946)
		Away from home combined	(-0.38 , 0.44)	0.04(0.8583)	0.13(0.5518)
Cotinine-N-glucuronide (nmol/mg Creatinine)	Non-Weighted	Spouse at home	(NA , NA)	1.00(NA)	1.00(NA)
		Others at home	(-0.79 , 0.72)	-0.08(0.8631)	0.36(0.4271)
		At home combined	(-0.48 , 0.79)	0.27(0.4890)	0.45(0.2220)
		Work	(-0.99 , 0.74)	-0.76(0.2378)	-0.40(0.6000)
		Vehicles	(-0.30 , 1.00)	0.93(0.0704)	0.32(0.6838)
		Other places	(-0.25 , 0.58)	0.20(0.3882)	0.28(0.2151)
		Away from home combined	(-0.32 , 0.46)	0.09(0.6858)	0.10(0.6317)
	Weighted	Spouse at home	(NA , NA)	1.00(NA)	1.00(NA)
		Others at home	(-0.74 , 0.77)	0.04(0.9349)	0.36(0.4271)
		At home combined	(-0.24 , 0.88)	0.50(0.1670)	0.52(0.1524)
		Work	(-0.99 , 0.82)	-0.66(0.3402)	-0.40(0.6000)
		Vehicles	(-0.25 , 1.00)	0.94(0.0638)	0.20(0.8000)
		Other places	(-0.37 , 0.49)	0.07(0.7519)	0.24(0.2918)
		Away from home combined	(-0.36 , 0.43)	0.04(0.8602)	0.07(0.7429)

^a Non-Weighted refers to the number of hours exposed to environmental tobacco smoke. For others at home, spouse at home, and at home combined, Weighted refers to the number of hours exposed to environmental tobacco smoke times the number of cigarettes smoked. For work, vehicles, other places, and away from home combined, weighted refers to the number of hours exposed to environmental tobacco smoke times the intensity (1=mild, 2=moderate, 3=severe) of smoke.

^b Away from home combined refers to exposure from at least one of the following: work, vehicles, other places. At home combined refers to at least one of the following: spouse at home, others at home.

^c 95% confidence interval for the correlation coefficient.

PM3006438349

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

14.2 Statistical Comparison of Biomarkers of Exposure

14.2.1 Overall Comparison Between Smokers and Non-Smokers

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-1
Statistical Comparison Between Smokers and Non-Smokers of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 1 of 14)

Biomarker: Acetonitrile ((ng/mL)/2) Analytical Lab: Madison

Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	313.81, 219.47	178.65, 97.51	
	SD, SE	322.285, 45.578	287.366, 35.643	
	MEDIAN	201.20	90.66	
	MIN, MAX	51.48, 1500.00	30.00, 1500.00	
	5%, 95%	75.16, 1089.74	30.00, 812.94	
	# of BLQ/ALQ Values	1/1	16/1	
Week 2	N	48	65	0.0002
	MEAN, GEO MEAN	357.78, 245.18	179.27, 115.61	
	SD, SE	332.195, 47.948	176.528, 21.896	
	MEDIAN	247.22	104.08	
	MIN, MAX	30.00, 1500.00	30.00, 756.74	
	5%, 95%	54.06, 1002.96	30.00, 610.62	
	# of BLQ/ALQ Values	1/2	12/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	544.89, 343.31	206.46, 133.78	
	SD, SE	576.013, 84.929	219.008, 27.165	
	MEDIAN	311.35	126.23	
	MIN, MAX	46.59, 2000.00	30.00, 1168.91	
	5%, 95%	76.49, 2000.00	30.00, 619.94	
	# of BLQ/ALQ Values	0/5	10/0	
Week 6	N	42	65	0.0004
	MEAN, GEO MEAN	439.65, 287.66	224.64, 133.92	
	SD, SE	421.896, 65.100	232.664, 28.858	
	MEDIAN	284.89	119.94	
	MIN, MAX	31.68, 1500.00	30.00, 947.36	
	5%, 95%	97.44, 1406.38	30.00, 670.92	
	# of BLQ/ALQ Values	0/1	13/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	409.36, 326.55	197.26, 159.57	
	SD, SE	270.039, 38.189	135.413, 16.796	
	MEDIAN	352.45	156.31	
	MIN, MAX	82.80, 1084.24	30.00, 701.92	
	5%, 95%	86.83, 1006.07	44.47, 452.36	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-1
Statistical Comparison Between Smokers and Non-Smokers of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 2 of 14)

Biomarker: Acetonitrile ((nmol/L)/2) Analytical Lab: Madison

Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	7650.8, 5350.7	4355.5, 2377.2	
	SD, SE	7857.31, 1111.19	7005.98, 868.99	
	MEDIAN	4905.3	2210.3	
	MIN, MAX	1255.1, 36570.0	731.4, 36570.0	
	5%, 95%	1832.4, 26567.9	731.4, 19819.5	
	# of BLQ/ALQ Values	1/1	16/1	
Week 2	N	48	65	0.0002
	MEAN, GEO MEAN	8722.7, 5977.6	4370.5, 2818.5	
	SD, SE	8098.92, 1168.98	4303.74, 533.81	
	MEDIAN	6027.1	2537.5	
	MIN, MAX	731.4, 36570.0	731.4, 18449.3	
	5%, 95%	1318.0, 24452.2	731.4, 14886.9	
	# of BLQ/ALQ Values	1/2	12/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	13284.4, 8369.8	5033.4, 3261.6	
	SD, SE	14043.21, 2070.56	5339.41, 662.27	
	MEDIAN	7590.7	3077.5	
	MIN, MAX	1135.9, 48760.0	731.4, 28498.0	
	5%, 95%	1864.8, 48760.0	731.4, 15114.1	
	# of BLQ/ALQ Values	0/5	10/0	
Week 6	N	42	65	0.0004
	MEAN, GEO MEAN	10718.6, 7013.0	5476.8, 3265.0	
	SD, SE	10285.83, 1587.14	5672.36, 703.57	
	MEDIAN	6945.6	2924.1	
	MIN, MAX	772.4, 36570.0	731.4, 23096.6	
	5%, 95%	2375.6, 34287.5	731.4, 16357.0	
	# of BLQ/ALQ Values	0/1	13/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	9980.1, 7961.1	4809.1, 3890.3	
	SD, SE	6583.55, 931.05	3301.38, 409.49	
	MEDIAN	8592.6	3810.7	
	MIN, MAX	2018.6, 26433.8	731.4, 17112.8	
	5%, 95%	2116.9, 24527.9	1084.1, 11028.6	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438352

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-1
Statistical Comparison Between Smokers and Non-Smokers of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 3 of 14)

Biomarker: Acetonitrile ((ng/mL)/cigarette per day) ²		Analytical Lab: Madison		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	24.91, 16.86		
	SD, SE	25.207, 3.565		
	MEDIAN	14.34		
	MIN, MAX	3.39, 116.91		
	5%, 95%	5.47, 84.16		
	# of BLQ/ALQ Values	1/1		
Week 2	N	48		NA
	MEAN, GEO MEAN	32.28, 19.21		
	SD, SE	42.578, 6.146		
	MEDIAN	15.81		
	MIN, MAX	3.93, 205.14		
	5%, 95%	5.98, 150.00		
	# of BLQ/ALQ Values	1/2		
Week 3	N	46		NA
	MEAN, GEO MEAN	56.90, 27.36		
	SD, SE	81.200, 11.972		
	MEDIAN	21.09		
	MIN, MAX	4.25, 333.33		
	5%, 95%	7.09, 250.00		
	# of BLQ/ALQ Values	0/5		
Week 6	N	42		NA
	MEAN, GEO MEAN	47.33, 21.54		
	SD, SE	108.798, 16.788		
	MEDIAN	18.74		
	MIN, MAX	3.17, 703.19		
	5%, 95%	5.17, 127.61		
	# of BLQ/ALQ Values	0/1		
Overall*	N	50		NA
	MEAN, GEO MEAN	39.94, 26.59		
	SD, SE	45.691, 6.462		
	MEDIAN	28.87		
	MIN, MAX	4.35, 264.63		
	5%, 95%	7.46, 129.96		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438353

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-1
Statistical Comparison Between Smokers and Non-Smokers of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 4 of 14)

Biomarker: Acetonitrile ((nmol/L)/cigarette per day/2)		Analytical Lab: Madison		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	607.2, 411.0		
	SD, SE	614.52, 86.91		
	MEDIAN	349.5		
	MIN, MAX	82.7, 2850.2		
	5%, 95%	133.3, 2051.9		
	# of BLQ/ALQ Values	1/1		
Week 2	N	48		NA
	MEAN, GEO MEAN	787.0, 468.2		
	SD, SE	1038.05, 149.83		
	MEDIAN	385.4		
	MIN, MAX	95.9, 5001.3		
	5%, 95%	145.7, 3657.0		
	# of BLQ/ALQ Values	1/2		
Week 3	N	46		NA
	MEAN, GEO MEAN	1387.2, 667.2		
	SD, SE	1979.68, 291.89		
	MEDIAN	514.0		
	MIN, MAX	103.6, 8126.7		
	5%, 95%	172.7, 6095.0		
	# of BLQ/ALQ Values	0/5		
Week 6	N	42		NA
	MEAN, GEO MEAN	1153.9, 525.1		
	SD, SE	2652.49, 409.29		
	MEDIAN	456.7		
	MIN, MAX	77.2, 17143.8		
	5%, 95%	126.1, 3111.1		
	# of BLQ/ALQ Values	0/1		
Overall*	N	50		NA
	MEAN, GEO MEAN	973.7, 648.3		
	SD, SE	1113.95, 157.54		
	MEDIAN	703.7		
	MIN, MAX	106.1, 6451.6		
	5%, 95%	181.7, 3168.4		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438354

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-1
Statistical Comparison Between Smokers and Non-Smokers of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 5 of 14)

Biomarker: 3-Aminobiphenyl-Hb adduct (pg/g hemoglobin) Analytical Lab: Harrogate				
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	49	65	<.0001
	MEAN, GEO MEAN	3.80, 2.70	0.59, 0.54	
	SD, SE	3.377, 0.482	0.511, 0.063	
	MEDIAN	2.58	0.50	
	MIN, MAX	0.50, 15.03	0.50, 4.59	
	5%, 95%	0.87, 10.43	0.50, 0.77	
	# of BLQ/ALQ Values	2/0	53/0	
Week 6	N	42	65	<.0001
	MEAN, GEO MEAN	5.36, 2.93	0.59, 0.55	
	SD, SE	9.783, 1.510	0.336, 0.042	
	MEDIAN	3.11	0.50	
	MIN, MAX	0.50, 63.34	0.50, 2.46	
	5%, 95%	0.50, 12.65	0.50, 1.35	
	# of BLQ/ALQ Values	3/0	59/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	4.39, 2.89	0.59, 0.56	
	SD, SE	5.147, 0.728	0.303, 0.038	
	MEDIAN	2.79	0.50	
	MIN, MAX	0.50, 32.18	0.50, 2.55	
	5%, 95%	0.81, 13.14	0.50, 1.09	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438355

Final Draft: 22 October 2003

Page 386 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-1
Statistical Comparison Between Smokers and Non-Smokers of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 6 of 14)

Biomarker: 3-Aminobiphenyl-Hb adduct ((pg/g hemoglobin)/cigarette per day)		Analytical Lab: Harrogate	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	49	
	MEAN, GEO MEAN	0.27, 0.21	
	SD, SE	0.225, 0.032	
	MEDIAN	0.21	
	MIN, MAX	0.06, 1.17	
	5%, 95%	0.06, 0.57	
	# of BLQ/ALQ Values	2/0	
Week 6	N	42	
	MEAN, GEO MEAN	1.05, 0.22	
	SD, SE	4.858, 0.750	
	MEDIAN	0.18	
	MIN, MAX	0.03, 31.67	
	5%, 95%	0.05, 1.05	
	# of BLQ/ALQ Values	3/0	
Overall*	N	50	
	MEAN, GEO MEAN	0.60, 0.23	
	SD, SE	2.242, 0.317	
	MEDIAN	0.22	
	MIN, MAX	0.05, 16.01	
	5%, 95%	0.06, 1.11	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438356

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-1
Statistical Comparison Between Smokers and Non-Smokers of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 7 of 14)

Biomarker: 4-Aminobiphenyl-Hb adduct (pg/g hemoglobin)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	49	65	<.0001
	MEAN, GEO MEAN	34.39, 28.34	7.28, 6.51	
	SD, SE	21.781, 3.112	3.713, 0.460	
	MEDIAN	28.94	6.55	
	MIN, MAX	5.35, 100.50	2.49, 23.25	
	5%, 95%	8.56, 87.23	3.12, 13.59	
	# of BLQ/ALQ Values	0/0	0/0	
Week 6	N	42	65	< .0001
	MEAN, GEO MEAN	59.01, 37.81	8.81, 7.96	
	SD, SE	120.309, 18.564	4.559, 0.566	
	MEDIAN	38.15	7.50	
	MIN, MAX	7.27, 808.80	4.09, 27.86	
	5%, 95%	9.56, 90.32	4.36, 16.50	
	# of BLQ/ALQ Values	0/0	0/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	44.31, 33.14	8.05, 7.35	
	SD, SE	56.254, 7.956	3.826, 0.475	
	MEDIAN	34.25	7.02	
	MIN, MAX	6.31, 408.68	3.62, 22.96	
	5%, 95%	11.43, 82.02	3.88, 15.04	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438357

Final Draft: 22 October 2003

Page 388 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-1
Statistical Comparison Between Smokers and Non-Smokers of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 8 of 14)

Biomarker: 4-Aminobiphenyl-Hb adduct ((pg/g hemoglobin)/cigarette per day)		Analytical Lab: Harrogate	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	49	
	MEAN, GEO MEAN	2.79, 2.20	
	SD, SE	2.710, 0.387	
	MEDIAN	2.17	
	MIN, MAX	0.59, 18.14	
	5%, 95%	0.90, 6.43	
	# of BLQ/ALQ Values	0/0	
Week 6	N	42	
	MEAN, GEO MEAN	12.99, 2.83	
	SD, SE	62.106, 9.583	
	MEDIAN	2.38	
	MIN, MAX	0.95, 404.40	
	5%, 95%	1.29, 8.15	
	# of BLQ/ALQ Values	0/0	
Overall*	N	50	
	MEAN, GEO MEAN	7.07, 2.62	
	SD, SE	28.615, 4.047	
	MEDIAN	2.19	
	MIN, MAX	0.90, 203.63	
	5%, 95%	1.16, 8.27	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438358

Final Draft: 22 October 2003

Page 389 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-1
Statistical Comparison Between Smokers and Non-Smokers of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 9 of 14)

Biomarker: Carboxyhemoglobin (% saturation) Analytical Lab: CCLS				
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	4.4, 3.3	0.4, 0.4	
	SD, SE	3.14, 0.44	0.17, 0.02	
	MEDIAN	4.0	0.3	
	MIN, MAX	0.3, 14.8	0.3, 1.0	
	5%, 95%	0.9, 11.3	0.3, 0.7	
	# of BLQ/ALQ Values	1/0	39/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	4.0, 2.8	0.4, 0.3	
	SD, SE	3.01, 0.43	0.16, 0.02	
	MEDIAN	3.4	0.3	
	MIN, MAX	0.3, 13.3	0.3, 1.1	
	5%, 95%	0.3, 9.8	0.3, 0.8	
	# of BLQ/ALQ Values	3/0	47/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	4.7, 3.6	0.5, 0.4	
	SD, SE	3.03, 0.45	0.50, 0.06	
	MEDIAN	4.0	0.3	
	MIN, MAX	0.3, 11.3	0.3, 2.8	
	5%, 95%	0.7, 10.4	0.3, 1.6	
	# of BLQ/ALQ Values	1/0	38/0	
Week 6	N	41	65	<.0001
	MEAN, GEO MEAN	4.7, 3.5	0.4, 0.4	
	SD, SE	2.96, 0.46	0.20, 0.03	
	MEDIAN	4.1	0.3	
	MIN, MAX	0.3, 13.9	0.3, 1.3	
	5%, 95%	0.4, 9.2	0.3, 0.8	
	# of BLQ/ALQ Values	2/0	34/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	4.4, 3.3	0.4, 0.4	
	SD, SE	2.90, 0.41	0.19, 0.02	
	MEDIAN	4.0	0.4	
	MIN, MAX	0.3, 12.2	0.3, 1.3	
	5%, 95%	0.7, 9.8	0.3, 0.8	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438359

Final Draft: 22 October 2003

Page 390 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-1
Statistical Comparison Between Smokers and Non-Smokers of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 10 of 14)

Biomarker: Carboxyhemoglobin ((% saturation)/cigarette per day)		Analytical Lab: CCLS	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	0.3, 0.3	
	SD, SE	0.42, 0.06	
	MEDIAN	0.2	
	MIN, MAX	0.1, 3.0	
	5%, 95%	0.1, 0.8	
	# of BLQ/ALQ Values	1/0	
Week 2	N	49	
	MEAN, GEO MEAN	0.3, NA	
	SD, SE	0.60, 0.09	
	MEDIAN	0.2	
	MIN, MAX	0.0, 4.3	
	5%, 95%	0.1, 0.5	
	# of BLQ/ALQ Values	3/0	
Week 3	N	46	
	MEAN, GEO MEAN	0.4, 0.3	
	SD, SE	0.35, 0.05	
	MEDIAN	0.3	
	MIN, MAX	0.1, 2.3	
	5%, 95%	0.1, 0.9	
	# of BLQ/ALQ Values	1/0	
Week 6	N	41	
	MEAN, GEO MEAN	0.5, 0.3	
	SD, SE	1.07, 0.17	
	MEDIAN	0.3	
	MIN, MAX	0.1, 7.0	
	5%, 95%	0.1, 0.7	
	# of BLQ/ALQ Values	2/0	
Overall*	N	50	
	MEAN, GEO MEAN	0.4, 0.3	
	SD, SE	0.58, 0.08	
	MEDIAN	0.3	
	MIN, MAX	0.1, 4.2	
	5%, 95%	0.1, 0.7	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438360

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-1
Statistical Comparison Between Smokers and Non-Smokers of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 11 of 14)

Biomarker: 3-Aminobiphenyl-Hb adduct (pg/g hemoglobin)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	3	8	0.6831
	MEAN, GEO MEAN	0.70, 0.70	1.44, 0.93	
	SD, SE	0.000, 0.000	2.082, 0.736	
	MEDIAN	0.70	0.70	
	MIN, MAX	0.70, 0.70	0.70, 6.59	
	5%, 95%	0.70, 0.70	0.70, 6.59	
	# of BLQ/ALQ Values	3/0	7/0	
Week 6	N	3	8	1.0000
	MEAN, GEO MEAN	0.70, 0.70	0.70, 0.70	
	SD, SE	0.000, 0.000	0.000, 0.000	
	MEDIAN	0.70	0.70	
	MIN, MAX	0.70, 0.70	0.70, 0.70	
	5%, 95%	0.70, 0.70	0.70, 0.70	
	# of BLQ/ALQ Values	3/0	8/0	
Overall*	N	5	8	0.5271
	MEAN, GEO MEAN	0.70, 0.70	1.07, 0.86	
	SD, SE	0.000, 0.000	1.043, 0.369	
	MEDIAN	0.70	0.70	
	MIN, MAX	0.70, 0.70	0.70, 3.65	
	5%, 95%	0.70, 0.70	0.70, 3.65	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438361

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-1
Statistical Comparison Between Smokers and Non-Smokers of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 12 of 14)

Biomarker: 3-Aminobiphenyl-Hb adduct ((pg/g hemoglobin)/cigarette per day)		Analytical Lab: INBIFO	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	3	
	MEAN, GEO MEAN	0.07, 0.07	
	SD, SE	0.042, 0.024	
	MEDIAN	0.06	
	MIN, MAX	0.04, 0.12	
	5%, 95%	0.04, 0.12	
	# of BLQ/ALQ Values	3/0	
Week 6	N	3	
	MEAN, GEO MEAN	0.10, 0.08	
	SD, SE	0.074, 0.043	
	MEDIAN	0.07	
	MIN, MAX	0.04, 0.18	
	5%, 95%	0.04, 0.18	
	# of BLQ/ALQ Values	3/0	
Overall*	N	5	
	MEAN, GEO MEAN	0.08, 0.07	
	SD, SE	0.059, 0.026	
	MEDIAN	0.06	
	MIN, MAX	0.04, 0.18	
	5%, 95%	0.04, 0.18	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438362

Final Draft: 22 October 2003

Page 393 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-1
Statistical Comparison Between Smokers and Non-Smokers of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 13 of 14)

Biomarker: 4-Aminobiphenyl-Hb adduct (pg/g hemoglobin)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	7	8	0.0015
	MEAN, GEO MEAN	33.31, 31.47	10.42, 9.82	
	SD, SE	13.624, 5.150	4.045, 1.430	
	MEDIAN	29.87	9.68	
	MIN, MAX	19.77, 62.63	6.74, 18.39	
	5%, 95%	19.77, 62.63	6.74, 18.39	
	# of BLQ/ALQ Values	0/0	0/0	
Week 6	N	7	8	0.0032
	MEAN, GEO MEAN	32.57, 28.28	11.30, 10.58	
	SD, SE	21.523, 8.135	4.479, 1.584	
	MEDIAN	27.83	9.93	
	MIN, MAX	16.85, 78.25	6.90, 19.24	
	5%, 95%	16.85, 78.25	6.90, 19.24	
	# of BLQ/ALQ Values	0/0	0/0	
Overall*	N	8	8	0.0009
	MEAN, GEO MEAN	32.48, 30.80	10.86, 10.35	
	SD, SE	11.676, 4.128	3.648, 1.290	
	MEDIAN	29.20	9.86	
	MIN, MAX	18.31, 54.06	6.99, 16.69	
	5%, 95%	18.31, 54.06	6.99, 16.69	

^a P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438363

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-1
Statistical Comparison Between Smokers and Non-Smokers of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 14 of 14)

Biomarker: 4-Aminobiphenyl-Hb adduct ((pg/g hemoglobin)/cigarette per day)		Analytical Lab: INBIFO	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	7	
	MEAN, GEO MEAN	4.61, 3.07	
	SD, SE	5.135, 1.941	
	MEDIAN	2.30	
	MIN, MAX	1.00, 15.66	
	5%, 95%	1.00, 15.66	
	# of BLQ/ALQ Values	0/0	
Week 6	N	7	
	MEAN, GEO MEAN	2.72, 2.20	
	SD, SE	2.048, 0.774	
	MEDIAN	2.43	
	MIN, MAX	0.89, 6.96	
	5%, 95%	0.89, 6.96	
	# of BLQ/ALQ Values	0/0	
Overall*	N	8	
	MEAN, GEO MEAN	3.62, 2.81	
	SD, SE	3.281, 1.160	
	MEDIAN	2.59	
	MIN, MAX	1.33, 11.31	
	5%, 95%	1.33, 11.31	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438364

Final Draft: 22 October 2003

Page 395 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 1 of 264)

Biomarker: NNAL (pg/24hr)		Analytical Lab: Madison		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	249287.700, 181853.367	11565.751, 10175.939	
	SD, SE	180186.7708, 25482.2575	6083.1888, 754.5267	
	MEDIAN	224364.000	9420.000	
	MIN, MAX	8460.000, 852355.000	3180.000, 30796.800	
	5%, 95%	23940.000, 649460.000	4800.000, 22800.000	
	# of BLQ/ALQ Values	2/0	61/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	278384.265, 210748.456	14031.600, 12142.720	
	SD, SE	174391.9368, 25712.6883	9362.8824, 1161.3226	
	MEDIAN	241481.000	12000.000	
	MIN, MAX	6288.000, 781704.000	4500.000, 57240.000	
	5%, 95%	52440.000, 558700.000	5940.000, 28440.000	
	# of BLQ/ALQ Values	1/0	61/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	259455.192, 199546.451	12798.675, 11568.878	
	SD, SE	160409.3654, 22685.3100	6104.9573, 757.2268	
	MEDIAN	239327.000	11190.000	
	MIN, MAX	7374.000, 589956.000	3840.000, 32310.000	
	5%, 95%	47776.000, 584078.900	6450.000, 24998.400	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438365

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 2 of 264)

Biomarker: NNAL (pmol/24hr)		Analytical Lab: Madison		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	1191.595, 869.259	55.284, 48.641	
	SD, SE	861.2928, 121.8052	29.0777, 3.6066	
	MEDIAN	1072.460	45.028	
	MIN, MAX	40.439, 4074.257	15.200, 147.209	
	5%, 95%	114.433, 3104.419	22.944, 108.984	
	# of BLQ/ALQ Values	2/0	61/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	1330.677, 1007.378	67.071, 58.042	
	SD, SE	833.5934, 122.9066	44.7546, 5.5511	
	MEDIAN	1154.279	57.360	
	MIN, MAX	30.057, 3736.545	21.510, 273.607	
	5%, 95%	250.663, 2670.586	28.393, 135.943	
	# of BLQ/ALQ Values	1/0	61/0	
Overall†	N	50	65	<.0001
	MEAN, GEO MEAN	1240.196, 953.832	61.178, 55.299	
	SD, SE	766.7568, 108.4358	29.1817, 3.6195	
	MEDIAN	1143.984	53.488	
	MIN, MAX	35.248, 2819.990	18.355, 154.442	
	5%, 95%	228.369, 2791.897	30.831, 119.493	

* P-value from Wilcoxon rank-sum test.

† Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438366

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 3 of 264)

Biomarker: NNAL ((pg/24hr)/cigarette per day)		Analytical Lab: Madison	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	18139.155, 13969.400	
	SD, SE	15044.5776, 2127.6246	
	MEDIAN	13949.909	
	MIN, MAX	2820.000, 85235.500	
	5%, 95%	5471.667, 46530.000	
	# of BLQ/ALQ Values	2/0	
Week 3	N	46	
	MEAN, GEO MEAN	20247.891, 16799.465	
	SD, SE	12691.7845, 1871.3015	
	MEDIAN	16864.236	
	MIN, MAX	2096.000, 64500.000	
	5%, 95%	6486.000, 41592.667	
	# of BLQ/ALQ Values	1/0	
Overall*	N	50	
	MEAN, GEO MEAN	19273.807, 15968.329	
	SD, SE	12317.2616, 1741.9238	
	MEDIAN	14798.998	
	MIN, MAX	2458.000, 62355.425	
	5%, 95%	5079.000, 42648.800	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438367

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 4 of 264)

Biomarker: NNAL ((pmol/24hr/cigarette per day) Analytical Lab: Madison				
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	50		NA
	MEAN, GEO MEAN	86.705, 66.774		
	SD, SE	71.9131, 10.1701		
	MEDIAN	66.681		
	MIN, MAX	13.480, 407.426		
	5%, 95%	26.155, 222.413		
	# of BLQ/ALQ Values	2/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	96.785, 80.301		
	SD, SE	60.6667, 8.9448		
	MEDIAN	80.612		
	MIN, MAX	10.019, 308.310		
	5%, 95%	31.003, 198.813		
	# of BLQ/ALQ Values	1/0		
Overall*	N	50		NA
	MEAN, GEO MEAN	92.129, 76.329		
	SD, SE	58.8765, 8.3264		
	MEDIAN	70.740		
	MIN, MAX	11.750, 298.059		
	5%, 95%	24.278, 203.862		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438368

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 5 of 264)

Biomarker: NNAL (pg/mg Creatinine)		Analytical Lab: Madison		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	219.163, 150.676	8.498, 7.145	
	SD, SE	181.7279, 25.7002	5.1547, 0.6394	
	MEDIAN	178.751	7.823	
	MIN, MAX	7.958, 813.359	1.932, 29.814	
	5%, 95%	13.730, 612.755	2.911, 17.143	
	# of BLQ/ALQ Values	2/0	61/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	226.894, 168.981	10.253, 8.514	
	SD, SE	159.6468, 23.5386	6.4647, 0.8019	
	MEDIAN	194.555	9.259	
	MIN, MAX	5.525, 724.324	2.158, 30.264	
	5%, 95%	47.240, 547.012	2.923, 23.715	
	# of BLQ/ALQ Values	1/0	61/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	223.061, 162.757	9.376, 8.147	
	SD, SE	167.5167, 23.6904	4.8825, 0.6056	
	MEDIAN	185.127	8.674	
	MIN, MAX	6.742, 768.842	2.364, 23.043	
	5%, 95%	34.373, 535.268	3.185, 18.495	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438369

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 6 of 264)

Biomarker: NNAL (pmol/mg Creatinine)		Analytical Lab: Madison		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	1.048, 0.720	0.041, 0.034	
	SD, SE	0.8687, 0.1229	0.0247, 0.0031	
	MEDIAN	0.855	0.037	
	MIN, MAX	0.038, 3.888	0.009, 0.143	
	5%, 95%	0.066, 2.929	0.014, 0.082	
	# of BLQ/ALQ Values	2/0	61/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	1.085, 0.807	0.049, 0.041	
	SD, SE	0.7631, 0.1125	0.0308, 0.0038	
	MEDIAN	0.930	0.044	
	MIN, MAX	0.026, 3.462	0.010, 0.145	
	5%, 95%	0.226, 2.615	0.014, 0.113	
	# of BLQ/ALQ Values	1/0	61/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	1.066, 0.778	0.045, 0.039	
	SD, SE	0.8008, 0.1132	0.0233, 0.0029	
	MEDIAN	0.885	0.042	
	MIN, MAX	0.032, 3.675	0.011, 0.110	
	5%, 95%	0.164, 2.559	0.015, 0.088	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438370

Final Draft: 22 October 2003

Page 401 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 7 of 264)

Biomarker: NNAL ((pg/mg Creatinine)/cigarette per day)		Analytical Lab: Madison		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	17.186, 11.574		
	SD, SE	22.5070, 3.1830		
	MEDIAN	11.512		
	MIN, MAX	2.653, 153.410		
	5%, 95%	3.199, 40.850		
	# of BLQ/ALQ Values	2/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	17.401, 13.470		
	SD, SE	14.5069, 2.1389		
	MEDIAN	12.185		
	MIN, MAX	1.842, 69.200		
	5%, 95%	4.470, 55.549		
	# of BLQ/ALQ Values	1/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	17.523, 13.046		
	SD, SE	16.9853, 2.4021		
	MEDIAN	11.915		
	MIN, MAX	2.248, 104.480		
	5%, 95%	4.078, 40.850		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438371

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 8 of 264)

Biomarker: NNAL ((pmol/mg Creatinine)/cigarette per day)		Analytical Lab: Madison		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	0.082, 0.055		
	SD, SE	0.1075, 0.0152		
	MEDIAN	0.055		
	MIN, MAX	0.013, 0.733		
	5%, 95%	0.015, 0.195		
	# of BLQ/ALQ Values	2/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	0.083, 0.064		
	SD, SE	0.0694, 0.0102		
	MEDIAN	0.058		
	MIN, MAX	0.009, 0.331		
	5%, 95%	0.021, 0.266		
	# of BLQ/ALQ Values	1/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	0.084, 0.063		
	SD, SE	0.0812, 0.0115		
	MEDIAN	0.057		
	MIN, MAX	0.011, 0.500		
	5%, 95%	0.020, 0.195		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438372

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 9 of 264)

Biomarker: NNAL (pg/mL)		Analytical Lab: Madison		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	150.0, 106.4	6.4, 6.2	
	SD, SE	107.23, 15.16	1.89, 0.23	
	MEDIAN	136.4	6.0	
	MIN, MAX	6.0, 484.5	6.0, 20.3	
	5%, 95%	11.4, 347.9	6.0, 8.5	
	# of BLQ/ALQ Values	2/0	61/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	161.2, 123.5	7.3, 6.5	
	SD, SE	109.14, 16.09	6.31, 0.78	
	MEDIAN	144.2	6.0	
	MIN, MAX	6.0, 485.1	6.0, 42.4	
	5%, 95%	28.2, 405.1	6.0, 10.5	
	# of BLQ/ALQ Values	1/0	61/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	153.7, 118.3	6.9, 6.5	
	SD, SE	101.02, 14.29	3.26, 0.40	
	MEDIAN	138.9	6.0	
	MIN, MAX	6.0, 474.5	6.0, 24.2	
	5%, 95%	20.9, 351.6	6.0, 11.4	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438373

Final Draft: 22 October 2003

Page 404 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 10 of 264)

Biomarker: NNAL (pmol/L)		Analytical Lab: Madison		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	717.2, 508.7	30.5, 29.8	
	SD, SE	512.56, 72.49	9.01, 1.12	
	MEDIAN	652.0	28.7	
	MIN, MAX	28.7, 2315.9	28.7, 97.0	
	5%, 95%	54.5, 1663.0	28.7, 40.6	
	# of BLQ/ALQ Values	2/0	61/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	770.5, 590.3	35.0, 31.2	
	SD, SE	521.68, 76.92	30.16, 3.74	
	MEDIAN	689.0	28.7	
	MIN, MAX	28.7, 2318.8	28.7, 202.7	
	5%, 95%	134.8, 1936.4	28.7, 50.2	
	# of BLQ/ALQ Values	1/0	61/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	734.7, 565.3	32.8, 31.1	
	SD, SE	482.89, 68.29	15.56, 1.93	
	MEDIAN	663.9	28.7	
	MIN, MAX	28.7, 2268.1	28.7, 115.7	
	5%, 95%	99.9, 1680.7	28.7, 54.3	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438374

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 11 of 264)

Biomarker: NNAL ((pg/mL)/cigarette per day)		Analytical Lab: Madison	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	11.0, 8.2	
	SD, SE	9.18, 1.30	
	MEDIAN	7.9	
	MIN, MAX	1.4, 47.0	
	5%, 95%	2.0, 27.8	
	# of BLQ/ALQ Values	2/0	
Week 3	N	46	
	MEAN, GEO MEAN	12.9, 9.8	
	SD, SE	10.89, 1.61	
	MEDIAN	10.3	
	MIN, MAX	2.0, 58.2	
	5%, 95%	2.8, 31.2	
	# of BLQ/ALQ Values	1/0	
Overall*	N	50	
	MEAN, GEO MEAN	12.2, 9.5	
	SD, SE	9.72, 1.37	
	MEDIAN	8.9	
	MIN, MAX	2.0, 47.0	
	5%, 95%	2.7, 36.7	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438375

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 12 of 264)

Biomarker: NNAL ((pmol/L)/cigarette per day)		Analytical Lab: Madison	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	52.5, 39.1	
	SD, SE	43.87, 6.20	
	MEDIAN	37.9	
	MIN, MAX	6.5, 224.7	
	5%, 95%	9.6, 132.6	
	# of BLQ/ALQ Values	2/0	
Week 3	N	46	
	MEAN, GEO MEAN	61.7, 47.1	
	SD, SE	52.02, 7.67	
	MEDIAN	49.0	
	MIN, MAX	9.6, 278.0	
	5%, 95%	13.5, 148.9	
	# of BLQ/ALQ Values	1/0	
Overall*	N	50	
	MEAN, GEO MEAN	58.1, 45.1	
	SD, SE	46.43, 6.57	
	MEDIAN	42.3	
	MIN, MAX	9.6, 224.7	
	5%, 95%	12.7, 175.1	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438376

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 13 of 264)

Biomarker: NNAL plus NNAL-gluc (pg/24hr)		Analytical Lab: Madison		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	49	65	<.0001
	MEAN, GEO MEAN	860758.551, 585425.280	14520.477, 10879.233	
	SD, SE	613472.2046, 87638.8864	22133.4597, 2745.3178	
	MEDIAN	785030.000	10140.000	
	MIN, MAX	8460.000, 2307613.000	3180.000, 181986.000	
	5%, 95%	37125.000, 2084332.500	4680.000, 21000.000	
	# of BLQ/ALQ Values	1/0	58/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	914457.937, 627898.806	14369.154, 12281.453	
	SD, SE	709365.3233, 104590.2109	10422.0126, 1292.6916	
	MEDIAN	783064.000	12000.000	
	MIN, MAX	6288.000, 4046406.000	4500.000, 61490.000	
	5%, 95%	97520.000, 1964160.000	6408.000, 28440.000	
	# of BLQ/ALQ Values	1/0	58/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	874401.621, 615371.996	14444.815, 11969.312	
	SD, SE	592615.0179, 83808.4196	12990.5012, 1611.2734	
	MEDIAN	839769.000	11070.000	
	MIN, MAX	7374.000, 2468208.000	3840.000, 97218.000	
	5%, 95%	66085.000, 2080140.250	6400.000, 30583.000	

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438377

Final Draft: 22 October 2003

Page 408 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 14 of 264)

Biomarker: NNAL plus NNAL-gluc (pmol/24hr)		Analytical Lab: Madison		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	49	65	<.0001
	MEAN, GEO MEAN	4114.426, 2798.333	69.408, 52.003	
	SD, SE	2932.3970, 418.9139	105.7979, 13.1226	
	MEDIAN	3752.443	48.469	
	MIN, MAX	40.439, 11030.390	15.200, 869.893	
	5%, 95%	177.458, 9963.109	22.370, 100.380	
	# of BLQ/ALQ Values	1/0	58/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	4371.109, 3001.357	68.685, 58.705	
	SD, SE	3390.7663, 499.9412	49.8172, 6.1791	
	MEDIAN	3743.046	57.360	
	MIN, MAX	30.057, 19341.821	21.510, 293.922	
	5%, 95%	466.146, 9388.685	30.630, 135.943	
	# of BLQ/ALQ Values	1/0	58/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	4179.640, 2941.479	69.046, 57.214	
	SD, SE	2832.6997, 400.6042	62.0946, 7.7019	
	MEDIAN	4014.096	52.915	
	MIN, MAX	35.248, 11798.035	18.355, 464.702	
	5%, 95%	315.887, 9943.070	30.592, 146.187	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438378

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 15 of 264)

Biomarker: NNAL plus NNAL-gluc ((pg/24hr)/cigarette per day)		Analytical Lab: Madison		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	49		NA
	MEAN, GEO MEAN	56456.734, 44404.705		
	SD, SE	38952.1879, 5564.5983		
	MEDIAN	50477.857		
	MIN, MAX	2820.000, 176718.500		
	5%, 95%	12565.000, 153840.867		
	# of BLQ/ALQ Values	1/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	62625.596, 50051.917		
	SD, SE	40626.0676, 5989.9869		
	MEDIAN	51940.813		
	MIN, MAX	2096.000, 192686.000		
	5%, 95%	18154.500, 138353.600		
	# of BLQ/ALQ Values	1/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	59627.475, 49291.845		
	SD, SE	34052.5998, 4815.7648		
	MEDIAN	51637.690		
	MIN, MAX	2458.000, 154712.800		
	5%, 95%	16521.250, 132624.738		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 16 of 264)

Biomarker: NNAL plus NNAL-gluc ((pmol/24hr)/cigarette per day)		Analytical Lab: Madison		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	49		NA
	MEAN, GEO MEAN	269.863, 212.255		
	SD, SE	186.1914, 26.5988		
	MEDIAN	241.284		
	MIN, MAX	13.480, 844.714		
	5%, 95%	60.061, 735.359		
	# of BLQ/ALQ Values	1/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	299.350, 239.248		
	SD, SE	194.1926, 28.6321		
	MEDIAN	248.277		
	MIN, MAX	10.019, 921.039		
	5%, 95%	86.779, 661.330		
	# of BLQ/ALQ Values	1/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	285.020, 235.616		
	SD, SE	162.7713, 23.0193		
	MEDIAN	246.829		
	MIN, MAX	11.750, 739.527		
	5%, 95%	78.972, 633.946		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438380

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 17 of 264)

Biomarker: NNAL plus NNAL-gluc (pg/mg Creatinine)		Analytical Lab: Madison		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	49	65	<.0001
	MEAN, GEO MEAN	738.054, 487.673	10.558, 7.638	
	SD, SE	585.2483, 83.6069	16.3892, 2.0328	
	MEDIAN	625.442	8.915	
	MIN, MAX	7.958, 2575.145	1.932, 134.956	
	5%, 95%	30.892, 2010.238	2.683, 17.699	
	# of BLQ/ALQ Values	1/0	58/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	721.933, 503.456	10.876, 8.612	
	SD, SE	524.1048, 77.2750	9.0374, 1.1210	
	MEDIAN	580.019	8.380	
	MIN, MAX	5.525, 2275.640	2.158, 53.767	
	5%, 95%	65.031, 2004.781	2.923, 30.000	
	# of BLQ/ALQ Values	1/0	58/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	726.768, 500.586	10.717, 8.491	
	SD, SE	532.2826, 75.2761	9.7162, 1.2051	
	MEDIAN	617.105	8.438	
	MIN, MAX	6.742, 2250.747	2.131, 70.371	
	5%, 95%	43.687, 1877.496	3.508, 27.562	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438381

Final Draft: 22 October 2003

Page 412 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 18 of 264)

Biomarker: NNAL plus NNAL-gluc (pmol/mg Creatinine)		Analytical Lab: Madison		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	49	65	<.0001
	MEAN, GEO MEAN	3.528, 2.331	0.050, 0.036	
	SD, SE	2.7975, 0.3996	0.0783, 0.0097	
	MEDIAN	2.990	0.043	
	MIN, MAX	0.038, 12.309	0.009, 0.645	
	5%, 95%	0.148, 9.609	0.013, 0.085	
	# of BLQ/ALQ Values	1/0	58/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	3.451, 2.406	0.052, 0.041	
	SD, SE	2.5053, 0.3694	0.0432, 0.0054	
	MEDIAN	2.773	0.040	
	MIN, MAX	0.026, 10.878	0.010, 0.257	
	5%, 95%	0.311, 9.583	0.014, 0.143	
	# of BLQ/ALQ Values	1/0	58/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	3.474, 2.393	0.051, 0.041	
	SD, SE	2.5443, 0.3598	0.0465, 0.0058	
	MEDIAN	2.950	0.041	
	MIN, MAX	0.032, 10.759	0.010, 0.337	
	5%, 95%	0.209, 8.975	0.017, 0.132	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438382

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 19 of 264)

Biomarker: NNAL plus NNAL-gluc ((pg/mg Creatinine)/cigarette per day) Analytical Lab: Madison			
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	49	
	MEAN, GEO MEAN	53.989, 36.990	
	SD, SE	73.1881, 10.4554	
	MEDIAN	40.489	
	MIN, MAX	2.653, 515.029	
	5%, 95%	8.053, 116.939	
	# of BLQ/ALQ Values	1/0	
Week 3	N	46	
	MEAN, GEO MEAN	52.624, 40.132	
	SD, SE	44.1283, 6.5064	
	MEDIAN	39.373	
	MIN, MAX	1.842, 235.969	
	5%, 95%	16.258, 155.193	
	# of BLQ/ALQ Values	1/0	
Overall*	N	50	
	MEAN, GEO MEAN	53.613, 40.164	
	SD, SE	54.9019, 7.7643	
	MEDIAN	41.836	
	MIN, MAX	2.248, 375.499	
	5%, 95%	13.016, 131.185	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438383

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 20 of 264)

Biomarker: NNAL plus NNAL-gluc ((pmol/mg Creatinine)/cigarette per day)		Analytical Lab: Madison		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	49		NA
	MEAN, GEO MEAN	0.258, 0.177		
	SD, SE	0.3498, 0.0500		
	MEDIAN	0.194		
	MIN, MAX	0.013, 2.462		
	5%, 95%	0.039, 0.559		
	# of BLQ/ALQ Values	1/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	0.252, 0.192		
	SD, SE	0.2109, 0.0311		
	MEDIAN	0.189		
	MIN, MAX	0.009, 1.128		
	5%, 95%	0.078, 0.742		
	# of BLQ/ALQ Values	1/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	0.257, 0.193		
	SD, SE	0.2624, 0.0371		
	MEDIAN	0.200		
	MIN, MAX	0.011, 1.795		
	5%, 95%	0.063, 0.627		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438384

Final Draft: 22 October 2003

Page 415 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 21 of 264)

Biomarker: NNAL plus NNAL-gluc (pg/mL)		Analytical Lab: Madison		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	49	65	<.0001
	MEAN, GEO MEAN	546.8, 341.2	9.5, 6.7	
	SD, SE	468.94, 66.99	22.78, 2.83	
	MEDIAN	475.2	6.0	
	MIN, MAX	6.0, 2045.7	6.0, 185.7	
	5%, 95%	16.5, 1604.2	6.0, 8.8	
	# of BLQ/ALQ Values	1/0	58/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	552.8, 367.9	7.4, 6.6	
	SD, SE	487.35, 71.86	6.14, 0.76	
	MEDIAN	426.6	6.0	
	MIN, MAX	6.0, 2223.3	6.0, 47.3	
	5%, 95%	53.0, 1721.9	6.0, 11.9	
	# of BLQ/ALQ Values	1/0	58/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	542.5, 366.0	8.5, 6.8	
	SD, SE	427.04, 60.39	12.25, 1.52	
	MEDIAN	433.9	6.0	
	MIN, MAX	6.0, 1663.1	6.0, 95.9	
	5%, 95%	34.8, 1471.5	6.0, 11.9	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438385

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 22 of 264)

Biomarker: NNAL plus NNAL-gluc (pmol/L)		Analytical Lab: Madison		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	49	65	<.0001
	MEAN, GEO MEAN	2613.5, 1631.1	45.7, 31.9	
	SD, SE	2241.53, 320.22	108.87, 13.50	
	MEDIAN	2271.5	28.7	
	MIN, MAX	28.7, 9778.4	28.7, 887.6	
	5%, 95%	78.9, 7668.1	28.7, 42.1	
	# of BLQ/ALQ Values	1/0	58/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	2642.5, 1758.6	35.3, 31.6	
	SD, SE	2329.54, 343.47	29.34, 3.64	
	MEDIAN	2038.9	28.7	
	MIN, MAX	28.7, 10627.4	28.7, 226.1	
	5%, 95%	253.3, 8230.7	28.7, 56.9	
	# of BLQ/ALQ Values	1/0	58/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	2592.9, 1749.4	40.5, 32.5	
	SD, SE	2041.22, 288.67	58.54, 7.26	
	MEDIAN	2074.0	28.7	
	MIN, MAX	28.7, 7949.4	28.7, 458.2	
	5%, 95%	166.1, 7033.6	28.7, 56.7	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 23 of 264)

Biomarker: NNAL plus NNAL-gluc ((pg/mL)/cigarette per day)		Analytical Lab: Madison	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	49	
	MEAN, GEO MEAN	36.0, 25.9	
	SD, SE	29.20, 4.17	
	MEDIAN	27.0	
	MIN, MAX	2.0, 128.6	
	5%, 95%	6.0, 95.6	
	# of BLQ/ALQ Values	1/0	
Week 3	N	46	
	MEAN, GEO MEAN	41.9, 29.3	
	SD, SE	41.76, 6.16	
	MEDIAN	24.0	
	MIN, MAX	2.0, 247.1	
	5%, 95%	10.0, 100.6	
	# of BLQ/ALQ Values	1/0	
Overall*	N	50	
	MEAN, GEO MEAN	39.2, 29.2	
	SD, SE	31.74, 4.49	
	MEDIAN	27.8	
	MIN, MAX	2.0, 168.1	
	5%, 95%	8.7, 98.1	
			P-value*

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438387

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 24 of 264)

Biomarker: NNAL plus NNAL-gluc ((pmol/L)/cigarette per day)		Analytical Lab: Madison	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	49	
	MEAN, GEO MEAN	172.1, 123.7	
	SD, SE	139.58, 19.94	
	MEDIAN	129.3	
	MIN, MAX	9.6, 614.6	
	5%, 95%	28.6, 456.7	
	# of BLQ/ALQ Values	1/0	
Week 3	N	46	
	MEAN, GEO MEAN	200.3, 140.2	
	SD, SE	199.60, 29.43	
	MEDIAN	114.5	
	MIN, MAX	9.6, 1180.9	
	5%, 95%	47.7, 481.1	
	# of BLQ/ALQ Values	1/0	
Overall*	N	50	
	MEAN, GEO MEAN	187.4, 139.7	
	SD, SE	151.69, 21.45	
	MEDIAN	132.8	
	MIN, MAX	9.6, 803.4	
	5%, 95%	41.5, 468.9	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438388

Final Draft: 22 October 2003

Page 419 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 25 of 264)

Biomarker: NNAL-O-glucuronide (pmol/L)		Analytical Lab: Madison		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	49	61	<.0001
	MEAN, GEO MEAN	1889.1, NA	18.1, NA	
	SD, SE	1803.06, 257.58	112.36, 14.39	
	MEDIAN	1564.5	0.0	
	MIN, MAX	0.0, 7462.5	0.0, 859.0	
	5%, 95%	35.9, 5782.8	0.0, 13.4	
	# of BLQ/ALQ Values	2/0	61/0	
Week 3	N	46	63	<.0001
	MEAN, GEO MEAN	1872.0, NA	3.8, NA	
	SD, SE	1907.93, 281.31	15.16, 1.91	
	MEDIAN	1352.5	0.0	
	MIN, MAX	0.0, 9536.6	0.0, 99.9	
	5%, 95%	35.4, 5911.9	0.0, 28.2	
	# of BLQ/ALQ Values	1/0	61/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	1859.5, NA	10.3, NA	
	SD, SE	1623.98, 229.67	55.10, 6.83	
	MEDIAN	1521.7	0.0	
	MIN, MAX	0.0, 5778.3	0.0, 429.5	
	5%, 95%	29.9, 5668.4	0.0, 28.0	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438389

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 26 of 264)

Biomarker: NNAL-O-glucuronide ((pmol/L)/cigarette per day) Analytical Lab: Madison			
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	49	
	MEAN, GEO MEAN	119.6, NA	
	SD, SE	103.95, 14.85	
	MEDIAN	85.8	
	MIN, MAX	0.0, 481.9	
	5%, 95%	16.1, 339.2	
	# of BLQ/ALQ Values	2/0	
Week 3	N	46	
	MEAN, GEO MEAN	138.6, NA	
	SD, SE	154.18, 22.73	
	MEDIAN	79.1	
	MIN, MAX	0.0, 902.9	
	5%, 95%	8.9, 350.2	
	# of BLQ/ALQ Values	1/0	
Overall*	N	50	
	MEAN, GEO MEAN	129.5, NA	
	SD, SE	112.33, 15.89	
	MEDIAN	90.0	
	MIN, MAX	0.0, 601.0	
	5%, 95%	10.4, 345.0	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438390

Final Draft: 22 October 2003

Page 421 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 27 of 264)

Biomarker: NNAL-O-glucuronide (pmol/24hr)		Analytical Lab: Madison		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	49	51	<.0001
	MEAN, GEO MEAN	2908.931, NA	18.258, NA	
	SD, SE	2273.5232, 324.7890	109.6835, 14.0435	
	MEDIAN	2416.280	0.000	
	MIN, MAX	0.000, 8788.668	0.000, 841.820	
	5%, 95%	98.725, 7630.840	0.000, 21.417	
	# of BLQ/ALQ Values	2/0	61/0	
Week 3	N	46	63	<.0001
	MEAN, GEO MEAN	3040.444, NA	7.137, NA	
	SD, SE	2849.3120, 420.1081	29.7623, 3.7497	
	MEDIAN	2468.524	0.000	
	MIN, MAX	0.000, 17356.612	0.000, 168.831	
	5%, 95%	65.136, 6821.100	0.000, 36.120	
	# of BLQ/ALQ Values	1/0	61/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	2940.092, NA	12.026, NA	
	SD, SE	2262.4910, 319.9646	55.0893, 6.8330	
	MEDIAN	2635.937	0.000	
	MIN, MAX	0.000, 10073.384	0.000, 420.910	
	5%, 95%	59.593, 7804.884	0.000, 80.217	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 28 of 264)

Biomarker: NNAL-O-glucuronide ((pmol/24hr)/cigarette per day)		Analytical Lab: Madison	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	49	
	MEAN, GEO MEAN	182.878, NA	
	SD, SE	131.3278, 18.7611	
	MEDIAN	156.941	
	MIN, MAX	0.000, 585.911	
	5%, 95%	33.903, 437.301	
	# of BLQ/ALQ Values	2/0	
Week 3	N	46	
	MEAN, GEO MEAN	202.567, NA	
	SD, SE	154.2054, 22.7363	
	MEDIAN	161.451	
	MIN, MAX	0.000, 826.505	
	5%, 95%	16.284, 505.646	
	# of BLQ/ALQ Values	1/0	
Overall*	N	50	
	MEAN, GEO MEAN	192.984, NA	
	SD, SE	121.2762, 17.1510	
	MEDIAN	166.137	
	MIN, MAX	0.000, 539.902	
	5%, 95%	27.239, 476.665	
			P-value ^a

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438392

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 29 of 264)

Biomarker: NNAL-O-glucuronide (pmol/mg Creatinine)		Analytical Lab: Madison		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	49	61	<.0001
	MEAN, GEO MEAN	2.466, NA	0.013, NA	
	SD, SE	2.0265, 0.2895	0.0808, 0.0103	
	MEDIAN	2.190	0.000	
	MIN, MAX	0.000, 8.643	0.000, 0.624	
	5%, 95%	0.082, 7.656	0.000, 0.009	
	# of BLQ/ALQ Values	2/0	61/0	
Week 3	N	46	63	<.0001
	MEAN, GEO MEAN	2.366, NA	0.006, NA	
	SD, SE	1.9608, 0.2891	0.0271, 0.0034	
	MEDIAN	1.823	0.000	
	MIN, MAX	0.000, 9.761	0.000, 0.171	
	5%, 95%	0.043, 6.216	0.000, 0.019	
	# of BLQ/ALQ Values	1/0	61/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	2.409, NA	0.009, NA	
	SD, SE	1.8649, 0.2637	0.0412, 0.0051	
	MEDIAN	1.986	0.000	
	MIN, MAX	0.000, 7.312	0.000, 0.312	
	5%, 95%	0.051, 6.478	0.000, 0.065	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438393

Final Draft: 22 October 2003

Page 424 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 30 of 264)

Biomarker: NNAL-O-glucuronide ((pmol/mg Creatinine)/cigarette per day) Analytical Lab: Madison

Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	49		NA
	MEAN, GEO MEAN	0.175, NA		
	SD, SE	0.2469, 0.0353		
	MEDIAN	0.119		
	MIN, MAX	0.000, 1.729		
	5%, 95%	0.022, 0.364		
	# of BLQ/ALQ Values	2/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	0.168, NA		
	SD, SE	0.1548, 0.0228		
	MEDIAN	0.119		
	MIN, MAX	0.000, 0.862		
	5%, 95%	0.011, 0.465		
	# of BLQ/ALQ Values	1/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	0.173, NA		
	SD, SE	0.1885, 0.0267		
	MEDIAN	0.133		
	MIN, MAX	0.000, 1.296		
	5%, 95%	0.023, 0.364		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234^a will be used as 1.234^a) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438394

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 31 of 264)

Biomarker: Cotinine (µg/24hr)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	1779.837, 1321.434	3.165, 2.104	
	SD, SE	1152.0055, 162.9182	4.4410, 0.5508	
	MEDIAN	1795.815	1.930	
	MIN, MAX	26.790, 6435.660	0.530, 27.900	
	5%, 95%	308.979, 3580.185	0.780, 12.160	
	# of BLQ/ALQ Values	0/0	49/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	1817.746, 1365.985	3.684, 2.287	
	SD, SE	1072.6598, 153.2371	7.4411, 0.9230	
	MEDIAN	1731.974	2.160	
	MIN, MAX	13.950, 4366.890	0.625, 59.280	
	5%, 95%	226.118, 3766.020	0.815, 9.804	
	# of BLQ/ALQ Values	0/0	47/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	1953.822, 1428.929	2.968, 2.232	
	SD, SE	1298.5750, 191.4644	3.6920, 0.4579	
	MEDIAN	1633.047	2.050	
	MIN, MAX	6.393, 5162.740	0.750, 25.870	
	5%, 95%	354.936, 4856.040	1.068, 7.188	
	# of BLQ/ALQ Values	0/0	50/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	1822.896, 1402.089	3.272, 2.312	
	SD, SE	1058.1876, 149.6503	4.4212, 0.5484	
	MEDIAN	1695.438	2.143	
	MIN, MAX	15.711, 4483.278	0.787, 30.043	
	5%, 95%	374.266, 3774.690	1.092, 12.202	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438395

Final Draft: 22 October 2003

Page 426 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 32 of 264)

Biomarker: Cotinine (nmol/24hr)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	10100.578, 7499.138	17.961, 11.943	
	SD, SE	6537.6311, 924.5607	25.2025, 3.1260	
	MEDIAN	10191.251	10.953	
	MIN, MAX	152.033, 36522.371	3.008, 158.333	
	5%, 95%	1753.456, 20317.550	4.427, 69.008	
	# of BLQ/ALQ Values	0/0	49/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	10315.706, 7751.966	20.906, 12.977	
	SD, SE	6087.3442, 869.6206	42.2284, 5.2378	
	MEDIAN	9828.952	12.258	
	MIN, MAX	79.166, 24782.101	3.547, 336.414	
	5%, 95%	1283.220, 21372.164	4.625, 55.638	
	# of BLQ/ALQ Values	0/0	47/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	11087.937, 8109.168	16.845, 12.667	
	SD, SE	7369.4133, 1086.5607	20.9521, 2.5988	
	MEDIAN	9267.542	11.634	
	MIN, MAX	36.280, 29298.550	4.256, 146.812	
	5%, 95%	2014.262, 27558.027	6.061, 40.792	
	# of BLQ/ALQ Values	0/0	50/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	10344.938, 7956.855	18.371, 13.119	
	SD, SE	6005.2150, 849.2657	25.0903, 3.1121	
	MEDIAN	9621.607	12.163	
	MIN, MAX	89.160, 25442.605	4.464, 170.496	
	5%, 95%	2123.957, 21421.368	6.195, 69.245	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438396

Final Draft: 22 October 2003

Page 427 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 33 of 264)

Biomarker: Cotinine ((pg/24hr)/cigarette per day) Analytical Lab: Harrogate			
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	130.879, 101.508	
	SD, SE	108.2704, 15.3117	
	MEDIAN	98.981	
	MIN, MAX	8.930, 643.566	
	5%, 95%	29.911, 304.113	
	# of BLQ/ALQ Values	0/0	
Week 2	N	49	
	MEAN, GEO MEAN	155.721, 110.210	
	SD, SE	190.7348, 27.2478	
	MEDIAN	114.398	
	MIN, MAX	4.650, 1308.045	
	5%, 95%	32.303, 342.365	
	# of BLQ/ALQ Values	0/0	
Week 3	N	46	
	MEAN, GEO MEAN	142.739, 113.905	
	SD, SE	86.5808, 12.7656	
	MEDIAN	118.942	
	MIN, MAX	2.131, 335.938	
	5%, 95%	46.306, 325.744	
	# of BLQ/ALQ Values	0/0	
Overall*	N	50	
	MEAN, GEO MEAN	141.944, 113.039	
	SD, SE	111.7605, 15.8053	
	MEDIAN	103.857	
	MIN, MAX	5.237, 671.319	
	5%, 95%	47.120, 299.233	
			NA

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438397

Final Draft: 22 October 2003

Page 428 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 34 of 264)

Biomarker: Cotinine ((nmol/24hr)/cigarette per day)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	742.740, 576.060		
	SD, SE	614.4343, 86.8941		
	MEDIAN	561.716		
	MIN, MAX	50.678, 3652.237		
	5%, 95%	169.746, 1725.843		
Week 2	# of BLQ/ALQ Values	0/0		NA
	N	49		
	MEAN, GEO MEAN	883.715, 625.443		
	SD, SE	1082.4199, 154.6314		
	MEDIAN	649.206		
	MIN, MAX	26.389, 7423.156		
Week 3	5%, 95%	183.317, 1942.924		NA
	# of BLQ/ALQ Values	0/0		
	N	46		
	MEAN, GEO MEAN	810.046, 646.409		
	SD, SE	491.3460, 72.4450		
	MEDIAN	674.991		
Overall ^b	MIN, MAX	12.093, 1906.445		NA
	5%, 95%	262.788, 1848.600		
	# of BLQ/ALQ Values	0/0		
	N	50		
	MEAN, GEO MEAN	805.529, 641.498		
	SD, SE	634.2410, 89.6952		
	MEDIAN	589.388		
	MIN, MAX	29.720, 3809.735		
	5%, 95%	267.406, 1698.146		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438398

Final Draft: 22 October 2003

Page 429 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 35 of 264)

Biomarker: Cotinine (µg/mg Creatinine)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	1.607, 1.095	0.002, NA	
	SD, SE	1.2214, 0.1727	0.0030, 0.0004	
	MEDIAN	1.401	0.001	
	MIN, MAX	0.025, 5.808	0.000, 0.020	
	5%, 95%	0.203, 3.903	0.000, 0.009	
	# of BLQ/ALQ Values	0/0	49/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	1.474, 1.055	0.003, NA	
	SD, SE	1.0867, 0.1552	0.0070, 0.0009	
	MEDIAN	1.263	0.002	
	MIN, MAX	0.016, 5.177	0.000, 0.057	
	5%, 95%	0.148, 3.337	0.000, 0.007	
	# of BLQ/ALQ Values	0/0	47/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	1.609, 1.147	0.002, NA	
	SD, SE	1.1859, 0.1749	0.0022, 0.0003	
	MEDIAN	1.333	0.002	
	MIN, MAX	0.006, 5.186	0.000, 0.014	
	5%, 95%	0.383, 4.005	0.001, 0.005	
	# of BLQ/ALQ Values	0/0	50/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	1.575, 1.138	0.002, NA	
	SD, SE	1.1231, 0.1588	0.0035, 0.0004	
	MEDIAN	1.305	0.002	
	MIN, MAX	0.016, 4.572	0.000, 0.026	
	5%, 95%	0.266, 3.886	0.001, 0.007	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438399

Final Draft: 22 October 2003

Page 430 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 36 of 264)

Biomarker: Cotinine (nmol/mg Creatinine)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	9.121, 6.214	0.013, NA	
	SD, SE	6.9314, 0.9802	0.0173, 0.0021	
	MEDIAN	7.951	0.006	
	MIN, MAX	0.142, 32.960	0.000, 0.114	
	5%, 95%	1.152, 22.150	0.000, 0.051	
	# of BLQ/ALQ Values	0/0	49/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	8.365, 5.987	0.017, NA	
	SD, SE	6.1668, 0.8810	0.0397, 0.0049	
	MEDIAN	7.168	0.011	
	MIN, MAX	0.091, 29.379	0.000, 0.323	
	5%, 95%	0.840, 18.937	0.000, 0.040	
	# of BLQ/ALQ Values	0/0	47/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	9.133, 6.511	0.012, NA	
	SD, SE	6.7302, 0.9923	0.0124, 0.0015	
	MEDIAN	7.565	0.011	
	MIN, MAX	0.034, 29.431	0.000, 0.079	
	5%, 95%	2.174, 22.728	0.006, 0.028	
	# of BLQ/ALQ Values	0/0	50/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	8.937, 6.454	0.014, NA	
	SD, SE	6.3738, 0.9014	0.0196, 0.0024	
	MEDIAN	7.403	0.009	
	MIN, MAX	0.089, 25.944	0.000, 0.149	
	5%, 95%	1.510, 22.053	0.004, 0.038	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438400

Final Draft: 22 October 2003

Page 431 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 37 of 264)

Biomarker: Cotinine (($\mu\text{g}/\text{mg}$ Creatinine)/cigarette per day)		Analytical Lab: Harrogate	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	0.129, 0.084	
	SD, SE	0.1723, 0.0244	
	MEDIAN	0.082	
	MIN, MAX	0.008, 1.162	
	5%, 95%	0.021, 0.366	
	# of BLQ/ALQ Values	0/0	
Week 2	N	49	
	MEAN, GEO MEAN	0.154, 0.085	
	SD, SE	0.3622, 0.0517	
	MEDIAN	0.076	
	MIN, MAX	0.005, 2.589	
	5%, 95%	0.023, 0.303	
	# of BLQ/ALQ Values	0/0	
Week 3	N	46	
	MEAN, GEO MEAN	0.125, 0.091	
	SD, SE	0.1146, 0.0169	
	MEDIAN	0.100	
	MIN, MAX	0.002, 0.580	
	5%, 95%	0.032, 0.321	
	# of BLQ/ALQ Values	0/0	
Overall*	N	50	
	MEAN, GEO MEAN	0.137, 0.092	
	SD, SE	0.2027, 0.0287	
	MEDIAN	0.094	
	MIN, MAX	0.005, 1.432	
	5%, 95%	0.034, 0.311	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438401

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 38 of 264)

Biomarker: Cotinine ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50		NA
	MEAN, GEO MEAN	0.732, 0.477		
	SD, SE	0.9777, 0.1383		
	MEDIAN	0.462		
	MIN, MAX	0.047, 6.592		
	5%, 95%	0.119, 2.078		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	0.871, 0.483		
	SD, SE	2.0554, 0.2936		
	MEDIAN	0.429		
	MIN, MAX	0.030, 14.690		
	5%, 95%	0.129, 1.721		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	0.709, 0.519		
	SD, SE	0.6501, 0.0959		
	MEDIAN	0.565		
	MIN, MAX	0.011, 3.292		
	5%, 95%	0.182, 1.821		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	0.776, 0.521		
	SD, SE	1.1504, 0.1627		
	MEDIAN	0.533		
	MIN, MAX	0.029, 8.127		
	5%, 95%	0.190, 1.767		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438402

Final Draft: 22 October 2003

Page 433 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 39 of 264)

Biomarker: Cotinine (ng/mL)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	1029.4, 773.3	1.7, 1.3	
	SD, SE	619.01, 87.54	2.09, 0.26	
	MEDIAN	919.4	1.0	
	MIN, MAX	18.2, 2626.8	1.0, 14.1	
	5%, 95%	226.0, 2263.4	1.0, 4.8	
	# of BLQ/ALQ Values	0/0	49/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	1154.8, 883.0	1.9, 1.3	
	SD, SE	788.02, 112.57	2.91, 0.36	
	MEDIAN	975.4	1.0	
	MIN, MAX	15.5, 4778.6	1.0, 20.8	
	5%, 95%	221.4, 2343.3	1.0, 4.1	
	# of BLQ/ALQ Values	0/0	47/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	1082.9, 837.2	1.5, 1.2	
	SD, SE	632.01, 93.19	2.42, 0.30	
	MEDIAN	998.4	1.0	
	MIN, MAX	6.1, 2858.1	1.0, 19.9	
	5%, 95%	257.2, 2346.7	1.0, 2.8	
	# of BLQ/ALQ Values	0/0	50/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	1076.8, 846.7	1.7, 1.3	
	SD, SE	616.60, 87.20	2.10, 0.26	
	MEDIAN	970.2	1.0	
	MIN, MAX	13.5, 3090.2	1.0, 13.9	
	5%, 95%	275.9, 1962.5	1.0, 4.1	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438403

Final Draft: 22 October 2003

Page 434 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 40 of 264)

Biomarker: Cotinine (nmol/L)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	5842.0, 4388.4	9.6, 7.3	
	SD, SE	3512.90, 496.80	11.88, 1.47	
	MEDIAN	5217.3	5.7	
	MIN, MAX	103.3, 14907.1	5.7, 80.0	
	5%, 95%	1282.6, 12844.8	5.7, 27.2	
	# of BLQ/ALQ Values	0/0	49/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	6553.5, 5010.8	10.6, 7.6	
	SD, SE	4472.01, 638.86	16.49, 2.04	
	MEDIAN	5535.4	5.7	
	MIN, MAX	88.0, 27118.6	5.7, 118.0	
	5%, 95%	1256.4, 13298.2	5.7, 23.3	
	# of BLQ/ALQ Values	0/0	47/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	6145.2, 4751.3	8.7, 6.8	
	SD, SE	3586.67, 528.83	13.73, 1.70	
	MEDIAN	5665.7	5.7	
	MIN, MAX	34.6, 16219.7	5.7, 112.9	
	5%, 95%	1459.6, 13317.5	5.7, 15.9	
	# of BLQ/ALQ Values	0/0	50/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	6110.8, 4805.3	9.6, 7.5	
	SD, SE	3499.18, 494.86	11.94, 1.48	
	MEDIAN	5505.8	5.7	
	MIN, MAX	76.8, 17537.1	5.7, 78.7	
	5%, 95%	1566.0, 11137.0	5.7, 23.5	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438404

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 41 of 264)

Biomarker: Cotinine ((ng/mL)/cigarette per day)		Analytical Lab: Harrogate	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	74.4, 59.4	
	SD, SE	52.18, 7.38	
	MEDIAN	58.2	
	MIN, MAX	6.3, 262.7	
	5%, 95%	15.1, 188.6	
	# of BLQ/ALQ Values	0/0	
Week 2	N	49	
	MEAN, GEO MEAN	98.3, 71.2	
	SD, SE	121.43, 17.35	
	MEDIAN	67.8	
	MIN, MAX	5.2, 843.9	
	5%, 95%	29.6, 238.9	
	# of BLQ/ALQ Values	0/0	
Week 3	N	46	
	MEAN, GEO MEAN	90.8, 66.7	
	SD, SE	91.22, 13.45	
	MEDIAN	62.9	
	MIN, MAX	2.0, 571.6	
	5%, 95%	25.3, 194.1	
	# of BLQ/ALQ Values	0/0	
Overall*	N	50	
	MEAN, GEO MEAN	87.2, 67.9	
	SD, SE	81.29, 11.50	
	MEDIAN	64.8	
	MIN, MAX	4.5, 538.8	
	5%, 95%	31.8, 161.5	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438405

Final Draft: 22 October 2003

Page 436 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 42 of 264)

Biomarker: Cotinine ((nmol/L)/cigarette per day) Analytical Lab: Harrogate			
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	422.4, 337.1	
	SD, SE	296.12, 41.88	
	MEDIAN	330.1	
	MIN, MAX	35.9, 1490.7	
	5%, 95%	85.7, 1070.4	
	# of BLQ/ALQ Values	0/0	
Week 2	N	49	
	MEAN, GEO MEAN	557.6, 404.3	
	SD, SE	689.09, 98.44	
	MEDIAN	385.0	
	MIN, MAX	29.3, 4789.2	
	5%, 95%	168.0, 1355.9	
	# of BLQ/ALQ Values	0/0	
Week 3	N	46	
	MEAN, GEO MEAN	515.3, 378.7	
	SD, SE	517.71, 76.33	
	MEDIAN	356.9	
	MIN, MAX	11.5, 3243.9	
	5%, 95%	143.8, 1101.4	
	# of BLQ/ALQ Values	0/0	
Overall*	N	50	
	MEAN, GEO MEAN	494.9, 385.2	
	SD, SE	461.35, 65.24	
	MEDIAN	367.7	
	MIN, MAX	25.6, 3057.8	
	5%, 95%	180.6, 916.8	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438406

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 43 of 264)

Biomarker: Cotinine-N-glucuronide (nmol/L)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	12245.232, 6153.631	7.692, NA	
	SD, SE	13823.3167, 1954.9122	18.2035, 2.2579	
	MEDIAN	6149.147	0.000	
	MIN, MAX	71.505, 58435.475	0.000, 121.445	
	5%, 95%	193.518, 44549.885	0.000, 38.023	
	# of BLQ/ALQ Values	0/0	49/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	14130.356, 7525.660	8.818, NA	
	SD, SE	15556.5168, 2222.3595	18.2860, 2.2681	
	MEDIAN	7567.613	1.135	
	MIN, MAX	73.775, 77152.193	0.000, 92.503	
	5%, 95%	310.423, 42263.995	0.000, 57.318	
	# of BLQ/ALQ Values	0/0	47/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	11201.759, 6697.690	5.553, NA	
	SD, SE	9178.1533, 1353.2449	12.2139, 1.5149	
	MEDIAN	8706.585	0.000	
	MIN, MAX	81.153, 37456.135	0.000, 78.883	
	5%, 95%	756.478, 27258.728	0.000, 22.700	
	# of BLQ/ALQ Values	0/0	50/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	12368.899, 7152.222	7.354, NA	
	SD, SE	11679.4403, 1651.7223	13.6122, 1.6884	
	MEDIAN	8028.612	0.946	
	MIN, MAX	75.478, 53864.641	0.000, 74.910	
	5%, 95%	430.165, 31626.019	0.000, 33.293	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438407

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 44 of 264)

Biomarker: Cotinine-N-glucuronide (nmol/L)/cigarette per day		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	762.287, 472.703		
	SD, SE	771.9750, 109.1737		
	MEDIAN	527.289		
	MIN, MAX	23.835, 3712.490		
	5%, 95%	64.506, 2470.157		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	967.011, 607.184		
	SD, SE	899.6229, 128.5176		
	MEDIAN	591.851		
	MIN, MAX	24.592, 3857.610		
	5%, 95%	126.571, 2367.300		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	871.974, 533.895		
	SD, SE	863.9490, 127.3823		
	MEDIAN	578.252		
	MIN, MAX	27.051, 3961.718		
	5%, 95%	100.391, 2846.864		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	864.434, 571.783		
	SD, SE	729.4937, 103.1660		
	MEDIAN	698.097		
	MIN, MAX	25.159, 3026.032		
	5%, 95%	128.640, 2522.024		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438408

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 45 of 264)

Biomarker: Cotinine-N-glucuronide (nmol/24hr)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	17584.204, 10515.717	12.227, NA	
	SD, SE	15317.1515, 2166.1723	25.2601, 3.1331	
	MEDIAN	13519.978	0.000	
	MIN, MAX	100.822, 68661.683	0.000, 106.872	
	5%, 95%	561.202, 52173.823	0.000, 75.621	
	# of BLQ/ALQ Values	0/0	49/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	18182.368, 11642.571	15.344, NA	
	SD, SE	14562.1275, 2080.3039	32.3372, 4.0109	
	MEDIAN	14973.828	1.396	
	MIN, MAX	66.398, 68665.452	0.000, 203.789	
	5%, 95%	523.023, 54491.407	0.000, 73.080	
	# of BLQ/ALQ Values	0/0	47/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	17809.284, 11430.892	9.953, NA	
	SD, SE	12417.3464, 1830.8378	21.2412, 2.6346	
	MEDIAN	16848.227	0.000	
	MIN, MAX	85.048, 48692.976	0.000, 105.328	
	5%, 95%	1043.940, 37176.403	0.000, 50.216	
	# of BLQ/ALQ Values	0/0	50/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	17588.204, 11451.596	12.508, NA	
	SD, SE	13197.5310, 1866.4127	22.7210, 2.8182	
	MEDIAN	15932.218	1.778	
	MIN, MAX	84.089, 57165.219	0.000, 104.966	
	5%, 95%	827.405, 46579.291	0.000, 50.161	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438409

Final Draft: 22 October 2003

Page 440 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 46 of 264)

Biomarker: Cotinine-N-glucuronide ((nmol/24hr)/cigarette per day)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	1127.149, 807.784		
	SD, SE	1016.3918, 143.7395		
	MEDIAN	855.081		
	MIN, MAX	33.607, 6051.885		
	5%, 95%	142.017, 3069.048		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	1313.513, 939.344		
	SD, SE	1175.2250, 167.8893		
	MEDIAN	1020.252		
	MIN, MAX	22.133, 6205.773		
	5%, 95%	271.996, 3833.600		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	1270.167, 911.195		
	SD, SE	899.0178, 132.5529		
	MEDIAN	1086.509		
	MIN, MAX	28.349, 4080.569		
	5%, 95%	173.990, 3033.231		
	# of BLQ/ALQ Values	0/0		
Overall*	N	50		NA
	MEAN, GEO MEAN	1232.649, 921.621		
	SD, SE	919.0081, 129.9674		
	MEDIAN	922.614		
	MIN, MAX	28.030, 5059.513		
	5%, 95%	249.511, 2716.257		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438410

Final Draft: 22 October 2003

Page 441 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 47 of 264)

Biomarker: Cotinine-N-glucuronide (nmol/mg Creatinine)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	13.335, 8.713	0.008, NA	
	SD, SE	9.4621, 1.3381	0.0174, 0.0022	
	MEDIAN	12.095	0.000	
	MIN, MAX	0.095, 37.108	0.000, 0.075	
	5%, 95%	0.507, 33.762	0.000, 0.055	
	# of BLQ/ALQ Values	0/0	49/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	13.437, 8.986	0.011, NA	
	SD, SE	10.4751, 1.4964	0.0269, 0.0033	
	MEDIAN	11.760	0.001	
	MIN, MAX	0.074, 53.877	0.000, 0.195	
	5%, 95%	0.522, 34.914	0.000, 0.043	
	# of BLQ/ALQ Values	0/0	47/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	13.808, 9.166	0.007, NA	
	SD, SE	10.2141, 1.5060	0.0144, 0.0018	
	MEDIAN	14.106	0.000	
	MIN, MAX	0.075, 49.743	0.000, 0.067	
	5%, 95%	1.668, 34.847	0.000, 0.035	
	# of BLQ/ALQ Values	0/0	50/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	13.481, 9.180	0.009, NA	
	SD, SE	9.5809, 1.3549	0.0167, 0.0021	
	MEDIAN	12.611	0.001	
	MIN, MAX	0.081, 38.906	0.000, 0.091	
	5%, 95%	0.809, 38.061	0.000, 0.047	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438411

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 48 of 264)

Biomarker: Cotinine-N-glucuronide ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	0.906, 0.670		
	SD, SE	0.7516, 0.1063		
	MEDIAN	0.648		
	MIN, MAX	0.032, 3.670		
	5%, 95%	0.169, 2.486		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	1.052, 0.725		
	SD, SE	1.1509, 0.1644		
	MEDIAN	0.656		
	MIN, MAX	0.025, 6.653		
	5%, 95%	0.244, 2.843		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	1.036, 0.731		
	SD, SE	0.9616, 0.1418		
	MEDIAN	0.754		
	MIN, MAX	0.025, 5.120		
	5%, 95%	0.209, 3.082		
	# of BLQ/ALQ Values	0/0		
Overall*	N	50		NA
	MEAN, GEO MEAN	1.004, 0.740		
	SD, SE	0.8814, 0.1246		
	MEDIAN	0.753		
	MIN, MAX	0.027, 4.364		
	5%, 95%	0.281, 2.594		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438412

Final Draft: 22 October 2003

Page 443 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 49 of 264)

Biomarker: Nicotine (µg/24hr)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	1745.037, 1070.295	4.817, 2.136	
	SD, SE	1430.1976, 202.2605	13.3902, 1.6608	
	MEDIAN	1417.225	1.850	
	MIN, MAX	18.048, 5245.860	0.330, 93.100	
	5%, 95%	83.814, 4727.375	0.800, 13.992	
	# of BLQ/ALQ Values	0/0	51/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	1806.112, 1170.199	7.050, 2.147	
	SD, SE	1358.1127, 194.0161	37.2887, 4.6251	
	MEDIAN	1573.750	2.000	
	MIN, MAX	10.980, 5904.527	0.625, 302.670	
	5%, 95%	94.792, 4729.200	0.815, 6.758	
	# of BLQ/ALQ Values	0/0	54/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	2033.500, 1264.500	2.387, 2.037	
	SD, SE	1625.9686, 239.7360	1.8384, 0.2280	
	MEDIAN	1632.768	2.000	
	MIN, MAX	5.450, 6614.080	0.750, 13.650	
	5%, 95%	161.699, 5668.540	0.990, 4.740	
	# of BLQ/ALQ Values	0/0	57/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	1827.982, 1226.585	4.751, 2.291	
	SD, SE	1277.8760, 180.7190	15.2674, 1.8937	
	MEDIAN	1696.911	2.143	
	MIN, MAX	11.493, 4824.558	0.793, 121.310	
	5%, 95%	130.092, 4297.933	0.980, 8.342	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438413

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 50 of 264)

Biomarker: Nicotine (nmol/24hr)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	10758.156, 6598.368	29.696, 13.171	
	SD, SE	8817.1680, 1246.9359	82.5504, 10.2391	
	MEDIAN	8737.192	11.405	
	MIN, MAX	111.266, 32340.727	3.267, 573.962	
	5%, 95%	516.713, 29144.267	4.932, 86.261	
	# of BLQ/ALQ Values	0/0	51/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	11134.681, 7214.277	43.463, 13.235	
	SD, SE	8372.7650, 1196.1093	229.8849, 28.5137	
	MEDIAN	9702.169	12.330	
	MIN, MAX	67.692, 36401.409	3.853, 1865.961	
	5%, 95%	584.393, 29155.518	5.024, 41.663	
	# of BLQ/ALQ Values	0/0	54/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	12536.527, 7795.640	14.714, 12.560	
	SD, SE	10024.0962, 1477.9724	11.3339, 1.4058	
	MEDIAN	10066.012	12.330	
	MIN, MAX	33.599, 40775.803	4.624, 84.152	
	5%, 95%	996.874, 34946.549	6.103, 29.222	
	# of BLQ/ALQ Values	0/0	57/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	11269.508, 7561.892	29.291, 14.125	
	SD, SE	7878.1057, 1114.1324	94.1236, 11.6746	
	MEDIAN	10461.455	13.214	
	MIN, MAX	70.852, 29743.402	4.891, 747.878	
	5%, 95%	802.015, 26496.759	6.042, 51.426	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438414

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 51 of 264)

Biomarker: Nicotine ($\mu\text{g}/24\text{hr}/\text{cigarette per day}$) Analytical Lab: Harrogate			
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	116.774, 82.217	
	SD, SE	102.3062, 14.4683	
	MEDIAN	91.850	
	MIN, MAX	6.016, 590.746	
	5%, 95%	16.763, 272.020	
	# of BLQ/ALQ Values	0/0	
Week 2	N	49	
	MEAN, GEO MEAN	153.863, 94.414	
	SD, SE	248.5400, 35.5057	
	MEDIAN	92.998	
	MIN, MAX	3.660, 1747.393	
	5%, 95%	16.394, 360.360	
	# of BLQ/ALQ Values	0/0	
Week 3	N	46	
	MEAN, GEO MEAN	135.489, 100.798	
	SD, SE	90.2543, 13.3073	
	MEDIAN	121.820	
	MIN, MAX	1.817, 422.898	
	5%, 95%	23.100, 275.895	
	# of BLQ/ALQ Values	0/0	
Overall*	N	50	
	MEAN, GEO MEAN	132.882, 100.253	
	SD, SE	123.8433, 17.5141	
	MEDIAN	116.709	
	MIN, MAX	3.831, 849.365	
	5%, 95%	39.378, 281.914	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438415

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 52 of 264)

Biomarker: Nicotine ((nmol/24hr)/cigarette per day)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	719.909, 506.866		
	SD, SE	630.7173, 89.1969		
	MEDIAN	566.254		
	MIN, MAX	37.089, 3641.947		
	5%, 95%	103.343, 1677.003		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	948.567, 582.061		
	SD, SE	1532.2484, 218.8926		
	MEDIAN	573.331		
	MIN, MAX	22.564, 10772.675		
	5%, 95%	101.072, 2221.619		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	835.292, 621.417		
	SD, SE	556.4178, 82.0393		
	MEDIAN	751.016		
	MIN, MAX	11.200, 2607.168		
	5%, 95%	142.411, 1700.894		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	819.216, 618.061		
	SD, SE	763.4933, 107.9743		
	MEDIAN	719.512		
	MIN, MAX	23.618, 5236.332		
	5%, 95%	242.766, 1737.999		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438416

Final Draft: 22 October 2003

Page 447 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 53 of 264)

Biomarker: Nicotine (µg/mg Creatinine)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	1.551, 0.887	0.003, NA	
	SD, SE	1.6269, 0.2301	0.0074, 0.0009	
	MEDIAN	1.072	0.001	
	MIN, MAX	0.017, 8.892	0.000, 0.044	
	5%, 95%	0.071, 5.001	0.000, 0.012	
	# of BLQ/ALQ Values	0/0	51/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	1.459, 0.903	0.006, NA	
	SD, SE	1.3786, 0.1969	0.0357, 0.0044	
	MEDIAN	1.262	0.001	
	MIN, MAX	0.012, 6.916	0.000, 0.289	
	5%, 95%	0.071, 4.633	0.000, 0.004	
	# of BLQ/ALQ Values	0/0	54/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	1.565, 1.015	0.002, NA	
	SD, SE	1.1600, 0.1710	0.0012, 0.0002	
	MEDIAN	1.471	0.001	
	MIN, MAX	0.005, 5.060	0.000, 0.008	
	5%, 95%	0.107, 4.177	0.000, 0.004	
	# of BLQ/ALQ Values	0/0	57/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	1.522, 0.990	0.004, NA	
	SD, SE	1.2602, 0.1782	0.0137, 0.0017	
	MEDIAN	1.351	0.002	
	MIN, MAX	0.011, 5.866	0.000, 0.111	
	5%, 95%	0.119, 4.066	0.001, 0.006	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438417

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 54 of 264)

Biomarker: Nicotine (nmol/mg Creatinine)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	9.559, 5.466	0.020, NA	
	SD, SE	10.0298, 1.4184	0.0459, 0.0057	
	MEDIAN	6.606	0.006	
	MIN, MAX	0.105, 54.819	0.000, 0.271	
	5%, 95%	0.438, 30.831	0.000, 0.074	
	# of BLQ/ALQ Values	0/0	51/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	8.998, 5.566	0.039, NA	
	SD, SE	8.4990, 1.2141	0.2199, 0.0273	
	MEDIAN	7.780	0.006	
	MIN, MAX	0.074, 42.637	0.000, 1.782	
	5%, 95%	0.438, 28.562	0.000, 0.025	
	# of BLQ/ALQ Values	0/0	54/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	9.650, 6.259	0.010, NA	
	SD, SE	7.1517, 1.0545	0.0076, 0.0009	
	MEDIAN	9.066	0.006	
	MIN, MAX	0.031, 31.195	0.000, 0.049	
	5%, 95%	0.660, 25.751	0.000, 0.025	
	# of BLQ/ALQ Values	0/0	57/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	9.382, 6.109	0.023, NA	
	SD, SE	7.7691, 1.0987	0.0841, 0.0104	
	MEDIAN	8.328	0.010	
	MIN, MAX	0.070, 36.164	0.000, 0.682	
	5%, 95%	0.734, 25.067	0.004, 0.039	

^a P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438418

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 55 of 264)

Biomarker: Nicotine ((µg/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	0.121, 0.068		
	SD, SE	0.2468, 0.0349		
	MEDIAN	0.071		
	MIN, MAX	0.006, 1.778		
	5%, 95%	0.014, 0.191		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	0.161, 0.073		
	SD, SE	0.4856, 0.0694		
	MEDIAN	0.065		
	MIN, MAX	0.004, 3.458		
	5%, 95%	0.013, 0.244		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	0.110, 0.081		
	SD, SE	0.0761, 0.0112		
	MEDIAN	0.091		
	MIN, MAX	0.002, 0.358		
	5%, 95%	0.016, 0.255		
	# of BLQ/ALQ Values	0/0		
Overall†	N	50		NA
	MEAN, GEO MEAN	0.130, 0.081		
	SD, SE	0.2565, 0.0363		
	MEDIAN	0.081		
	MIN, MAX	0.004, 1.865		
	5%, 95%	0.023, 0.227		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

† Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438419

Final Draft: 22 October 2003

Page 450 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 56 of 264)

Biomarker: Nicotine ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	0.747, 0.420		
	SD, SE	1.5220, 0.2152		
	MEDIAN	0.438		
	MIN, MAX	0.035, 10.964		
	5%, 95%	0.088, 1.178		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	0.991, 0.449		
	SD, SE	2.9937, 0.4277		
	MEDIAN	0.400		
	MIN, MAX	0.025, 21.319		
	5%, 95%	0.079, 1.504		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	0.675, 0.499		
	SD, SE	0.4695, 0.0692		
	MEDIAN	0.564		
	MIN, MAX	0.010, 2.207		
	5%, 95%	0.099, 1.570		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	0.800, 0.500		
	SD, SE	1.5812, 0.2236		
	MEDIAN	0.499		
	MIN, MAX	0.023, 11.497		
	5%, 95%	0.143, 1.399		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438420

Final Draft: 22 October 2003

Page 451 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 57 of 264)

Biomarker: Nicotine (ng/mL)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	1141.8, 626.3	2.2, 1.3	
	SD, SE	1210.89, 171.25	4.25, 0.53	
	MEDIAN	649.3	1.0	
	MIN, MAX	12.8, 6329.6	1.0, 24.5	
	5%, 95%	45.8, 3752.0	1.0, 6.8	
	# of BLQ/ALQ Values	0/0	51/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	1245.5, 756.4	2.9, 1.3	
	SD, SE	1251.38, 178.77	13.05, 1.62	
	MEDIAN	835.4	1.0	
	MIN, MAX	12.2, 6634.3	1.0, 106.2	
	5%, 95%	83.5, 3489.6	1.0, 4.3	
	# of BLQ/ALQ Values	0/0	54/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	1166.7, 740.9	1.2, 1.1	
	SD, SE	933.84, 137.69	1.24, 0.15	
	MEDIAN	911.3	1.0	
	MIN, MAX	5.2, 3630.2	1.0, 10.5	
	5%, 95%	131.0, 3006.4	1.0, 1.7	
	# of BLQ/ALQ Values	0/0	57/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	1167.2, 745.0	2.1, 1.3	
	SD, SE	1017.73, 143.93	5.34, 0.66	
	MEDIAN	815.5	1.0	
	MIN, MAX	10.1, 5531.4	1.0, 42.7	
	5%, 95%	69.4, 2950.7	1.0, 3.3	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438421

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 58 of 264)

Biomarker: Nicotine (nmol/L)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	7039.3, 3861.3	13.5, 8.1	
	SD, SE	7465.15, 1055.73	26.18, 3.25	
	MEDIAN	4002.7	6.2	
	MIN, MAX	78.9, 39022.0	6.2, 151.0	
	5%, 95%	282.4, 23131.1	6.2, 41.9	
	# of BLQ/ALQ Values	0/0	51/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	7678.6, 4663.2	18.2, 7.7	
	SD, SE	7714.75, 1102.11	80.42, 9.97	
	MEDIAN	5150.2	6.2	
	MIN, MAX	75.2, 40900.5	6.2, 634.7	
	5%, 95%	514.8, 21513.4	6.2, 26.5	
	# of BLQ/ALQ Values	0/0	54/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	7192.6, 4567.8	7.6, 6.8	
	SD, SE	5757.14, 848.84	7.61, 0.94	
	MEDIAN	5618.2	6.2	
	MIN, MAX	32.1, 22380.2	6.2, 64.7	
	5%, 95%	807.6, 18534.5	6.2, 10.5	
	# of BLQ/ALQ Values	0/0	57/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	7196.0, 4592.7	13.1, 8.1	
	SD, SE	6274.31, 887.32	32.91, 4.08	
	MEDIAN	5077.4	6.2	
	MIN, MAX	62.1, 34100.9	6.2, 263.2	
	5%, 95%	427.6, 18191.3	6.2, 20.3	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438422

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 59 of 264)

Biomarker: Nicotine ((ng/mL)/cigarette per day)		Analytical Lab: Harrogate	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	74.5, 48.1	
	SD, SE	73.23, 10.36	
	MEDIAN	53.8	
	MIN, MAX	4.3, 312.7	
	5%, 95%	9.2, 287.7	
	# of BLQ/ALQ Values	0/0	
Week 2	N	49	
	MEAN, GEO MEAN	103.7, 61.0	
	SD, SE	166.97, 23.85	
	MEDIAN	55.7	
	MIN, MAX	4.1, 1127.4	
	5%, 95%	15.7, 307.9	
	# of BLQ/ALQ Values	0/0	
Week 3	N	46	
	MEAN, GEO MEAN	85.9, 59.0	
	SD, SE	76.09, 11.22	
	MEDIAN	66.1	
	MIN, MAX	1.7, 374.9	
	5%, 95%	14.7, 242.0	
	# of BLQ/ALQ Values	0/0	
Overall*	N	50	
	MEAN, GEO MEAN	86.4, 60.6	
	SD, SE	93.76, 13.26	
	MEDIAN	55.0	
	MIN, MAX	3.4, 603.3	
	5%, 95%	20.1, 210.8	
			NA

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438423

Final Draft: 22 October 2003

Page 454 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2 1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 60 of 264)

Biomarker: Nicotine ((nmol/L)/cigarette per day) Analytical Lab: Harrogate			
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	459.0, 296.6	
	SD, SE	451.47, 63.85	
	MEDIAN	331.6	
	MIN, MAX	26.3, 1927.6	
	5%, 95%	56.5, 1773.7	
	# of BLQ/ALQ Values	0/0	
Week 2	N	49	
	MEAN, GEO MEAN	639.3, 376.3	
	SD, SE	1029.33, 147.05	
	MEDIAN	343.3	
	MIN, MAX	25.1, 6950.1	
	5%, 95%	97.0, 1898.3	
	# of BLQ/ALQ Values	0/0	
Week 3	N	46	
	MEAN, GEO MEAN	529.4, 364.1	
	SD, SE	469.06, 69.16	
	MEDIAN	407.3	
	MIN, MAX	10.7, 2311.4	
	5%, 95%	90.3, 1492.0	
	# of BLQ/ALQ Values	0/0	
Overall	N	50	
	MEAN, GEO MEAN	532.9, 373.4	
	SD, SE	578.08, 81.75	
	MEDIAN	339.1	
	MIN, MAX	20.7, 3719.4	
	5%, 95%	123.7, 1299.5	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438424

Final Draft: 22 October 2003

Page 455 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 61 of 264)

Biomarker: Nicotine-N-glucuronide (nmol/L)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	40	62	<.0001
	MEAN, GEO MEAN	2978.211, 1359.261	1.810, NA	
	SD, SE	3802.1449, 543.1636	4.2784, 0.5434	
	MEDIAN	1405.004	0.000	
	MIN, MAX	17.879, 17624.502	0.000, 22.811	
	5%, 95%	71.514, 11547.045	0.000, 9.248	
	# of BLQ/ALQ Values	0/0	51/0	
Week 2	N	48	63	<.0001
	MEAN, GEO MEAN	3456.562, 1750.146	2.593, NA	
	SD, SE	4353.5928, 628.3870	12.6584, 1.5948	
	MEDIAN	1479.292	0.000	
	MIN, MAX	68.432, 25269.102	0.000, 99.257	
	5%, 95%	121.451, 10055.115	0.000, 9.864	
	# of BLQ/ALQ Values	0/0	54/0	
Week 3	N	45	65	<.0001
	MEAN, GEO MEAN	2802.102, 1441.503	1.328, NA	
	SD, SE	2424.2917, 361.3921	4.0898, 0.5073	
	MEDIAN	2594.232	0.000	
	MIN, MAX	12.330, 8494.754	0.000, 28.976	
	5%, 95%	27.126, 8015.733	0.000, 6.165	
	# of BLQ/ALQ Values	0/0	57/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	2971.557, 1586.553	1.914, NA	
	SD, SE	3164.2230, 447.4887	5.4016, 0.6700	
	MEDIAN	1558.718	0.000	
	MIN, MAX	22.503, 14522.685	0.000, 36.579	
	5%, 95%	98.640, 9135.914	0.000, 7.707	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438425

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1.2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 62 of 264)

Biomarker: Nicotine-N-glucuronide ((nmol/L)/cigarette per day)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	49		NA
	MEAN, GEO MEAN	186.474, 106.209		
	SD, SE	226.2210, 32.3173		
	MEDIAN	100.816		
	MIN, MAX	5.960, 1036.735		
	5%, 95%	18.187, 720.449		
Week 2	# of BLQ/ALQ Values	0/0		NA
	N	48		
	MEAN, GEO MEAN	237.481, 137.093		
	SD, SE	267.3848, 38.5937		
	MEDIAN	139.734		
	MIN, MAX	4.562, 1263.455		
Week 3	5%, 95%	33.044, 730.384		NA
	# of BLQ/ALQ Values	0/0		
	N	45		
	MEAN, GEO MEAN	213.931, 113.039		
	SD, SE	198.0646, 29.5257		
	MEDIAN	145.682		
Overall*	MIN, MAX	1.192, 674.143		NA
	5%, 95%	9.042, 555.261		
	# of BLQ/ALQ Values	0/0		
	N	50		
	MEAN, GEO MEAN	206.210, 127.824		
	SD, SE	200.0369, 28.2895		
	MEDIAN	126.274		
	MIN, MAX	7.501, 756.966		
	5%, 95%	25.616, 705.631		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438426

Final Draft: 22 October 2003

Page 457 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 63 of 264)

Biomarker: Nicotine-N-glucuronide (nmol/24hr)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	49	62	<.0001
	MEAN, GEO MEAN	4098.496, 2293.981	3.042, NA	
	SD, SE	4073.6525, 581.9504	7.0213, 0.8917	
	MEDIAN	2740.959	0.000	
	MIN, MAX	25.209, 22030.628	0.000, 29.594	
	5%, 95%	162.756, 10788.304	0.000, 22.042	
	# of BLQ/ALQ Values	0/0	51/0	
Week 2	N	48	63	<.0001
	MEAN, GEO MEAN	4409.210, 2738.292	6.347, NA	
	SD, SE	4279.9893, 617.7632	35.7513, 4.5042	
	MEDIAN	3529.189	0.000	
	MIN, MAX	177.318, 22489.501	0.000, 282.882	
	5%, 95%	294.258, 11807.486	0.000, 14.886	
	# of BLQ/ALQ Values	0/0	54/0	
Week 3	N	45	65	<.0001
	MEAN, GEO MEAN	4437.910, 2471.845	2.326, NA	
	SD, SE	3364.7124, 501.5817	6.2367, 0.7736	
	MEDIAN	4005.325	0.000	
	MIN, MAX	17.262, 12487.288	0.000, 37.669	
	5%, 95%	52.296, 10485.827	0.000, 14.303	
	# of BLQ/ALQ Values	0/0	57/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	4172.890, 2585.250	3.898, NA	
	SD, SE	3505.6233, 495.7700	13.5723, 1.6834	
	MEDIAN	3084.908	0.000	
	MIN, MAX	26.819, 15441.801	0.000, 104.041	
	5%, 95%	199.791, 11219.242	0.000, 18.618	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438427

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 64 of 264)

Biomarker: Nicotine-N-glucuronide ((nmol/24hr)/cigarette per day)		Analytical Lab: Harrogate	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	49	
	MEAN, GEO MEAN	266.383, 179.244	
	SD, SE	263.2107, 37.6015	
	MEDIAN	183.997	
	MIN, MAX	8.403, 1295.919	
	5%, 95%	24.734, 837.161	
	# of BLQ/ALQ Values	0/0	
Week 2	N	48	
	MEAN, GEO MEAN	325.513, 214.496	
	SD, SE	356.1870, 51.4112	
	MEDIAN	200.027	
	MIN, MAX	19.617, 1880.171	
	5%, 95%	59.810, 1124.475	
	# of BLQ/ALQ Values	0/0	
Week 3	N	45	
	MEAN, GEO MEAN	317.537, 193.835	
	SD, SE	251.3426, 37.4679	
	MEDIAN	253.798	
	MIN, MAX	3.452, 929.600	
	5%, 95%	9.476, 741.273	
	# of BLQ/ALQ Values	0/0	
Overall*	N	50	
	MEAN, GEO MEAN	295.119, 209.508	
	SD, SE	251.5093, 35.5688	
	MEDIAN	189.633	
	MIN, MAX	8.940, 1230.708	
	5%, 95%	43.896, 767.442	
			NA

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438428

Final Draft: 22 October 2003

Page 459 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 65 of 264)

Biomarker: Nicotine-N-glucuronide (nmol/mg Creatinine)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	49	62	<.0001
	MEAN, GEO MEAN	3.019, 1.886	0.002, NA	
	SD, SE	2.3754, 0.3393	0.0048, 0.0006	
	MEDIAN	2.774	0.000	
	MIN, MAX	0.024, 12.113	0.000, 0.023	
	5%, 95%	0.135, 7.058	0.000, 0.012	
	# of BLQ/ALQ Values	0/0	51/0	
Week 2	N	48	63	<.0001
	MEAN, GEO MEAN	3.238, 2.097	0.006, NA	
	SD, SE	3.1048, 0.4481	0.0340, 0.0043	
	MEDIAN	2.471	0.000	
	MIN, MAX	0.153, 17.646	0.000, 0.270	
	5%, 95%	0.222, 6.805	0.000, 0.011	
	# of BLQ/ALQ Values	0/0	54/0	
Week 3	N	45	65	<.0001
	MEAN, GEO MEAN	3.372, 1.946	0.001, NA	
	SD, SE	2.5882, 0.3858	0.0034, 0.0004	
	MEDIAN	2.840	0.000	
	MIN, MAX	0.020, 10.645	0.000, 0.021	
	5%, 95%	0.056, 8.031	0.000, 0.008	
	# of BLQ/ALQ Values	0/0	57/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	3.169, 2.071	0.003, NA	
	SD, SE	2.4360, 0.3445	0.0122, 0.0015	
	MEDIAN	2.648	0.000	
	MIN, MAX	0.025, 10.339	0.000, 0.097	
	5%, 95%	0.190, 8.383	0.000, 0.009	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438429

Final Draft: 22 October 2003

Page 460 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 66 of 264)

Biomarker: Nicotine-N-glucuronide (nmol/mg Creatinine)/cigarette per day		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	49		NA
	MEAN, GEO MEAN	0.209, 0.147		
	SD, SE	0.1807, 0.0258		
	MEDIAN	0.139		
	MIN, MAX	0.008, 0.713		
	5%, 95%	0.031, 0.679		
	# of BLQ/ALQ Values	0/0		
Week 2	N	48		NA
	MEAN, GEO MEAN	0.258, 0.164		
	SD, SE	0.3189, 0.0460		
	MEDIAN	0.151		
	MIN, MAX	0.015, 1.647		
	5%, 95%	0.051, 0.882		
	# of BLQ/ALQ Values	0/0		
Week 3	N	45		NA
	MEAN, GEO MEAN	0.251, 0.153		
	SD, SE	0.2391, 0.0356		
	MEDIAN	0.165		
	MIN, MAX	0.004, 1.213		
	5%, 95%	0.008, 0.710		
	# of BLQ/ALQ Values	0/0		
Overall [*]	N	50		NA
	MEAN, GEO MEAN	0.237, 0.168		
	SD, SE	0.2165, 0.0306		
	MEDIAN	0.150		
	MIN, MAX	0.008, 1.065		
	5%, 95%	0.042, 0.590		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^{*} Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234) will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438430

Final Draft: 22 October 2003

Page 461 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 67 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (umol/mg Creatinine)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	68.467, 49.888	0.073, NA	
	SD, SE	43.2595, 6.1178	0.1188, 0.0147	
	MEDIAN	62.776	0.033	
	MIN, MAX	0.762, 171.322	0.000, 0.677	
	5%, 95%	8.068, 162.785	0.017, 0.340	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	69.207, 51.472	0.112, NA	
	SD, SE	45.1471, 6.4496	0.3667, 0.0455	
	MEDIAN	63.557	0.033	
	MIN, MAX	0.520, 177.245	0.000, 2.938	
	5%, 95%	10.256, 162.182	0.016, 0.209	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	71.913, 53.378	0.057, 0.039	
	SD, SE	46.2520, 6.8195	0.0733, 0.0091	
	MEDIAN	62.122	0.033	
	MIN, MAX	0.402, 204.112	0.011, 0.470	
	5%, 95%	14.475, 163.660	0.017, 0.174	
	# of BLQ/ALQ Values	0/0	0/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	69.731, 52.459	0.081, 0.044	
	SD, SE	43.5014, 6.1520	0.1621, 0.0201	
	MEDIAN	64.514	0.035	
	MIN, MAX	0.561, 182.343	0.011, 1.222	
	5%, 95%	10.933, 150.824	0.017, 0.255	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438431

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 68 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	4.963, 3.832		
	SD, SE	4.9765, 0.7038		
	MEDIAN	3.716		
	MIN, MAX	0.254, 34.264		
	5%, 95%	1.063, 12.963		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	6.265, 4.153		
	SD, SE	11.2861, 1.6123		
	MEDIAN	3.606		
	MIN, MAX	0.173, 81.091		
	5%, 95%	1.734, 11.330		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	5.325, 4.255		
	SD, SE	4.1846, 0.6170		
	MEDIAN	4.197		
	MIN, MAX	0.134, 23.794		
	5%, 95%	1.911, 10.156		
	# of BLQ/ALQ Values	0/0		
Overall*	N	50		NA
	MEAN, GEO MEAN	5.541, 4.232		
	SD, SE	6.4550, 0.9129		
	MEDIAN	4.068		
	MIN, MAX	0.187, 46.383		
	5%, 95%	1.877, 11.763		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438432

Final Draft: 22 October 2003

Page 463 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 69 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (mg/24hr)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	13.490, 9.768	0.017, 0.009	
	SD, SE	8.8670, 1.2540	0.0302, 0.0037	
	MEDIAN	13.234	0.007	
	MIN, MAX	0.131, 43.641	0.002, 0.157	
	5%, 95%	2.343, 27.701	0.003, 0.063	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	14.364, 10.818	0.024, 0.010	
	SD, SE	8.3444, 1.1921	0.0652, 0.0081	
	MEDIAN	14.064	0.008	
	MIN, MAX	0.075, 36.320	0.002, 0.499	
	5%, 95%	2.125, 33.028	0.003, 0.056	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	14.587, 10.799	0.014, 0.009	
	SD, SE	8.9934, 1.3260	0.0208, 0.0026	
	MEDIAN	13.707	0.007	
	MIN, MAX	0.074, 41.355	0.003, 0.136	
	5%, 95%	2.138, 32.720	0.004, 0.060	
	# of BLQ/ALQ Values	0/0	0/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	13.934, 10.577	0.018, 0.010	
	SD, SE	8.1211, 1.1485	0.0336, 0.0042	
	MEDIAN	13.706	0.008	
	MIN, MAX	0.093, 37.247	0.003, 0.222	
	5%, 95%	2.359, 27.579	0.003, 0.065	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234) will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438433

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 70 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites ((mg/24hr)/cigarette per day)		Analytical Lab: Harrogate	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	0.898, 0.750	
	SD, SE	0.5491, 0.0777	
	MEDIAN	0.786	
	MIN, MAX	0.044, 3.468	
	5%, 95%	0.273, 1.684	
	# of BLQ/ALQ Values	0/0	
Week 2	N	49	
	MEAN, GEO MEAN	1.118, 0.873	
	SD, SE	1.0211, 0.1459	
	MEDIAN	0.868	
	MIN, MAX	0.025, 6.647	
	5%, 95%	0.425, 2.761	
	# of BLQ/ALQ Values	0/0	
Week 3	N	46	
	MEAN, GEO MEAN	1.023, 0.861	
	SD, SE	0.5242, 0.0773	
	MEDIAN	0.982	
	MIN, MAX	0.025, 2.263	
	5%, 95%	0.420, 2.083	
	# of BLQ/ALQ Values	0/0	
Overall*	N	50	
	MEAN, GEO MEAN	1.008, 0.852	
	SD, SE	0.6034, 0.0853	
	MEDIAN	0.955	
	MIN, MAX	0.031, 3.585	
	5%, 95%	0.402, 1.810	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438434

Final Draft: 22 October 2003

Page 465 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 71 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (mg/mg Creatinine) Analytical Lab: Harrogate

Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	0.011, NA	0.000, NA	
	SD, SE	0.0071, 0.0010	0.0000, 0.0000	
	MEDIAN	0.010	0.000	
	MIN, MAX	0.000, 0.028	0.000, 0.000	
	5%, 95%	0.001, 0.026	0.000, 0.000	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	0.011, NA	0.000, NA	
	SD, SE	0.0073, 0.0010	0.0000, 0.0000	
	MEDIAN	0.010	0.000	
	MIN, MAX	0.000, 0.029	0.000, 0.000	
	5%, 95%	0.002, 0.026	0.000, 0.000	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	0.012, NA	0.000, NA	
	SD, SE	0.0075, 0.0011	0.0000, 0.0000	
	MEDIAN	0.010	0.000	
	MIN, MAX	0.000, 0.033	0.000, 0.000	
	5%, 95%	0.002, 0.027	0.000, 0.000	
	# of BLQ/ALQ Values	0/0	0/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	0.011, NA	0.000, NA	
	SD, SE	0.0071, 0.0010	0.0000, 0.0000	
	MEDIAN	0.010	0.000	
	MIN, MAX	0.000, 0.030	0.000, 0.000	
	5%, 95%	0.002, 0.024	0.000, 0.000	

^a P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438435

Final Draft: 22 October 2003

Page 466 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 72 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites ((mg/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	0.001, NA		
	SD, SE	0.0009, 0.0001		
	MEDIAN	0.001		
	MIN, MAX	0.000, 0.006		
	5%, 95%	0.000, 0.002		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	0.001, NA		
	SD, SE	0.0019, 0.0003		
	MEDIAN	0.001		
	MIN, MAX	0.000, 0.013		
	5%, 95%	0.000, 0.002		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	0.001, NA		
	SD, SE	0.0007, 0.0001		
	MEDIAN	0.001		
	MIN, MAX	0.000, 0.004		
	5%, 95%	0.000, 0.002		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	0.001, NA		
	SD, SE	0.0012, 0.0002		
	MEDIAN	0.001		
	MIN, MAX	0.000, 0.008		
	5%, 95%	0.000, 0.002		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438436

Final Draft: 22 October 2003

Page 467 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 73 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (nmol/24hr)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	83153.584, 60208.430	105.530, 54.081	
	SD, SE	54657.1229, 7729.6845	186.1554, 23.0897	
	MEDIAN	81571.855	44.994	
	MIN, MAX	807.495, 269008.088	13.634, 965.245	
	5%, 95%	14441.244, 170748.968	17.554, 388.382	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	88539.575, 66686.156	145.907, 62.366	
	SD, SE	51435.3073, 7347.9010	401.7923, 49.8362	
	MEDIAN	86689.522	49.426	
	MIN, MAX	463.520, 223877.537	12.603, 3077.553	
	5%, 95%	13096.445, 203586.824	17.436, 344.801	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	89914.281, 66565.555	85.407, 54.691	
	SD, SE	55436.2027, 8173.6222	128.0726, 15.8854	
	MEDIAN	84489.955	45.164	
	MIN, MAX	455.443, 254916.322	17.387, 838.565	
	5%, 95%	13178.209, 201686.943	22.786, 368.107	
	# of BLQ/ALQ Values	0/0	0/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	85889.343, 65200.410	112.281, 61.187	
	SD, SE	50059.2543, 7079.4476	207.3678, 25.7208	
	MEDIAN	84481.890	48.290	
	MIN, MAX	575.486, 229597.547	16.995, 1369.102	
	5%, 95%	14539.033, 169998.026	21.248, 401.405	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438437

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 74 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (nmol/24hr/cigarette per day)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	5533.031, 4625.021		
	SD, SE	3384.8254, 478.6866		
	MEDIAN	4847.574		
	MIN, MAX	269.165, 21374.817		
	5%, 95%	1679.783, 10379.541		
Week 2	# of BLQ/ALQ Values	0/0		NA
	N	49		
	MEAN, GEO MEAN	6892.223, 5380.358		
	SD, SE	6294.2825, 899.1832		
	MEDIAN	5348.991		
	MIN, MAX	154.507, 40974.206		
Week 3	5%, 95%	2619.289, 17016.199		NA
	# of BLQ/ALQ Values	0/0		
	N	46		
	MEAN, GEO MEAN	6307.558, 5306.163		
	SD, SE	3231.3395, 476.4350		
	MEDIAN	6055.057		
Overall*	MIN, MAX	151.814, 13950.879		NA
	5%, 95%	2586.936, 12841.396		
	# of BLQ/ALQ Values	0/0		
	N	50		
	MEAN, GEO MEAN	6214.769, 5252.453		
	SD, SE	3719.8748, 526.0697		
	MEDIAN	5888.948		
	MIN, MAX	191.829, 22102.107		
	5%, 95%	2475.432, 11156.032		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438438

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 75 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (nmol/L)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	53238.5, 35233.1	60.0, 33.2	
	SD, SE	44982.55, 6361.49	113.33, 14.06	
	MEDIAN	40007.4	22.9	
	MIN, MAX	572.7, 228943.1	17.1, 822.3	
	5%, 95%	5370.5, 128475.6	17.1, 184.7	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	62854.0, 43105.3	80.2, 36.4	
	SD, SE	51855.77, 7407.97	187.75, 23.29	
	MEDIAN	51484.6	23.5	
	MIN, MAX	515.0, 251547.8	17.1, 1079.8	
	5%, 95%	10010.5, 175038.6	17.1, 202.6	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	53561.0, 39002.7	45.9, 29.4	
	SD, SE	36385.03, 5364.68	82.65, 10.25	
	MEDIAN	45888.2	19.7	
	MIN, MAX	434.6, 161187.4	17.1, 645.0	
	5%, 95%	9549.4, 124561.5	17.1, 129.4	
	# of BLQ/ALQ Values	0/0	0/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	55931.5, 40417.7	62.1, 35.5	
	SD, SE	39513.50, 5588.05	105.04, 13.03	
	MEDIAN	44451.7	25.8	
	MIN, MAX	507.4, 177780.1	17.1, 555.8	
	5%, 95%	8324.0, 129505.1	17.1, 238.2	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438439

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 76 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites ((nmol/L)/cigarette per day)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	3482.0, 2706.5		
	SD, SE	2373.66, 335.69		
	MEDIAN	2775.4		
	MIN, MAX	190.9, 10706.3		
	5%, 95%	879.4, 8428.7		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	4789.0, 3477.8		
	SD, SE	4453.70, 636.24		
	MEDIAN	3777.3		
	MIN, MAX	171.7, 26435.0		
	5%, 95%	1287.1, 13281.7		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	4222.5, 3109.1		
	SD, SE	4026.79, 593.72		
	MEDIAN	3189.7		
	MIN, MAX	144.9, 24912.3		
	5%, 95%	1250.6, 11279.6		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	4157.8, 3236.2		
	SD, SE	3182.56, 450.08		
	MEDIAN	3658.4		
	MIN, MAX	169.2, 19091.7		
	5%, 95%	1248.9, 9143.4		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438440

Final Draft: 22 October 2003

Page 471 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 77 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (mg/L)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	8.6, 5.7	0.0, NA	
	SD, SE	7.30, 1.03	0.02, 0.00	
	MEDIAN	6.5	0.0	
	MIN, MAX	0.1, 37.1	0.0, 0.1	
	5%, 95%	0.9, 20.8	0.0, 0.0	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	10.2, 7.0	0.0, NA	
	SD, SE	8.41, 1.20	0.04, 0.00	
	MEDIAN	8.4	0.0	
	MIN, MAX	0.1, 40.8	0.0, 0.2	
	5%, 95%	1.6, 28.4	0.0, 0.0	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	8.7, 6.4	0.0, NA	
	SD, SE	5.90, 0.87	0.01, 0.00	
	MEDIAN	7.5	0.0	
	MIN, MAX	0.1, 26.1	0.0, 0.1	
	5%, 95%	1.5, 20.2	0.0, 0.0	
	# of BLQ/ALQ Values	0/0	0/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	9.1, 6.6	0.0, NA	
	SD, SE	6.41, 0.91	0.02, 0.00	
	MEDIAN	7.2	0.0	
	MIN, MAX	0.1, 28.8	0.0, 0.1	
	5%, 95%	1.4, 21.0	0.0, 0.0	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438441

Final Draft: 22 October 2003

Page 472 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 78 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites ((mg/L)/cigarette per day)		Analytical Lab: Harrogate	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	0.6, NA	
	SD, SE	0.39, 0.05	
	MEDIAN	0.5	
	MIN, MAX	0.0, 1.7	
	5%, 95%	0.1, 1.4	
	# of BLQ/ALQ Values	0/0	
Week 2	N	49	
	MEAN, GEO MEAN	0.8, NA	
	SD, SE	0.73, 0.10	
	MEDIAN	0.6	
	MIN, MAX	0.0, 4.3	
	5%, 95%	0.2, 2.2	
	# of BLQ/ALQ Values	0/0	
Week 3	N	46	
	MEAN, GEO MEAN	0.7, NA	
	SD, SE	0.65, 0.10	
	MEDIAN	0.6	
	MIN, MAX	0.0, 4.0	
	5%, 95%	0.2, 1.8	
	# of BLQ/ALQ Values	0/0	
Overall*	N	50	
	MEAN, GEO MEAN	0.7, NA	
	SD, SE	0.52, 0.07	
	MEDIAN	0.6	
	MIN, MAX	0.0, 3.1	
	5%, 95%	0.2, 1.5	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438442

Final Draft: 22 October 2003

Page 473 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 79 of 264)

Biomarker: Total 3-hydroxycotinine (µg/24hr)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	7831.126, 5355.823	8.345, 3.989	
	SD, SE	6001.9523, 848.8042	14.4819, 1.7963	
	MEDIAN	7518.912	3.000	
	MIN, MAX	80.370, 31233.615	0.800, 84.568	
	5%, 95%	795.900, 18631.252	1.140, 40.870	
	# of BLQ/ALQ Values	0/0	23/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	8569.600, 6203.499	11.570, 4.793	
	SD, SE	5412.4118, 773.2017	26.0279, 3.2284	
	MEDIAN	7610.064	3.150	
	MIN, MAX	48.420, 22147.192	1.000, 191.422	
	5%, 95%	842.508, 19677.560	1.148, 43.240	
	# of BLQ/ALQ Values	0/0	15/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	8483.711, 5938.857	7.990, 4.094	
	SD, SE	6120.1667, 902.3694	14.5318, 1.8024	
	MEDIAN	6586.053	3.219	
	MIN, MAX	52.295, 27434.900	1.068, 89.830	
	5%, 95%	1258.180, 18489.870	1.350, 44.835	
	# of BLQ/ALQ Values	0/0	25/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	8179.595, 5975.973	9.301, 4.690	
	SD, SE	5444.3965, 769.9539	16.0740, 1.9937	
	MEDIAN	6813.151	3.309	
	MIN, MAX	60.362, 23472.750	1.067, 97.065	
	5%, 95%	827.503, 20711.634	1.355, 42.982	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438443

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 80 of 264)

Biomarker: Total 3-hydroxycotinine (nmol/24hr) Analytical Lab: Harrogate				
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	40745.351, 27866.345	43.416, 20.752	
	SD, SE	31228.1578, 4416.3284	75.3495, 9.3459	
	MEDIAN	39120.900	15.609	
	MIN, MAX	418.165, 162508.499	4.162, 440.007	
	5%, 95%	4141.068, 96938.404	5.931, 212.647	
	# of BLQ/ALQ Values	0/0	23/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	44587.629, 32276.804	60.197, 24.940	
	SD, SE	28160.7785, 4022.9684	135.4230, 16.7972	
	MEDIAN	39595.163	16.389	
	MIN, MAX	251.929, 115231.840	5.203, 995.969	
	5%, 95%	4383.569, 102382.345	5.973, 224.978	
	# of BLQ/ALQ Values	0/0	15/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	44140.746, 30899.874	41.570, 21.301	
	SD, SE	31843.2274, 4695.0277	75.6090, 9.3781	
	MEDIAN	34267.231	16.748	
	MIN, MAX	272.091, 142847.845	5.557, 467.385	
	5%, 95%	6546.311, 96202.794	7.024, 233.277	
	# of BLQ/ALQ Values	0/0	25/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	42558.433, 31092.983	48.394, 24.402	
	SD, SE	28327.1955, 4006.0704	83.6332, 10.3734	
	MEDIAN	35448.825	17.217	
	MIN, MAX	314.062, 122128.717	5.550, 505.029	
	5%, 95%	4305.496, 107762.632	7.048, 223.634	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438444

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 81 of 264)

Biomarker: Total 3-hydroxycotinine ((µg/24hr)/cigarette per day)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	515.834, 411.417		
	SD, SE	327.1857, 46.2710		
	MEDIAN	470.075		
	MIN, MAX	26.790, 1738.618		
	5%, 95%	92.813, 1160.539		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	658.768, 500.509		
	SD, SE	565.0482, 80.7212		
	MEDIAN	529.433		
	MIN, MAX	16.140, 3571.898		
	5%, 95%	226.150, 1632.510		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	592.291, 473.406		
	SD, SE	368.0561, 54.2669		
	MEDIAN	506.162		
	MIN, MAX	17.432, 1676.349		
	5%, 95%	222.522, 1418.901		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	588.904, 478.775		
	SD, SE	363.6626, 51.4297		
	MEDIAN	499.268		
	MIN, MAX	20.121, 2030.196		
	5%, 95%	199.073, 1303.658		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438445

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 82 of 264)

Biomarker: Total 3-hydroxycotinine ((nmol/24hr)/cigarette per day)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	2683.886, 2140.604		
	SD, SE	1702.3472, 240.7483		
	MEDIAN	2445.801		
	MIN, MAX	139.388, 9046.030		
	5%, 95%	482.904, 6038.287		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	3427.569, 2604.150		
	SD, SE	2939.9458, 419.9923		
	MEDIAN	2754.642		
	MIN, MAX	83.976, 18584.583		
	5%, 95%	1176.658, 8493.950		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	3081.692, 2463.133		
	SD, SE	1914.9958, 282.3507		
	MEDIAN	2633.560		
	MIN, MAX	90.697, 8722.043		
	5%, 95%	1157.784, 7382.540		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	3064.067, 2491.068		
	SD, SE	1892.1364, 267.5885		
	MEDIAN	2597.689		
	MIN, MAX	104.687, 10563.111		
	5%, 95%	1035.779, 6782.931		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438446

Final Draft: 22 October 2003

Page 477 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 83 of 264)

Biomarker: Total 3-hydroxycotinine (µg/mg Creatinine)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	6.449, 4.438	0.006, NA	
	SD, SE	4.6629, 0.6594	0.0098, 0.0012	
	MEDIAN	5.375	0.002	
	MIN, MAX	0.076, 18.383	0.000, 0.052	
	5%, 95%	0.370, 15.997	0.001, 0.022	
	# of BLQ/ALQ Values	0/0	23/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	6.772, 4.788	0.008, NA	
	SD, SE	4.9259, 0.7037	0.0156, 0.0019	
	MEDIAN	5.554	0.002	
	MIN, MAX	0.054, 20.024	0.000, 0.099	
	5%, 95%	0.503, 18.134	0.001, 0.027	
	# of BLQ/ALQ Values	0/0	15/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	6.924, 4.762	0.005, 0.003	
	SD, SE	5.3191, 0.7843	0.0080, 0.0010	
	MEDIAN	5.015	0.002	
	MIN, MAX	0.046, 23.294	0.001, 0.050	
	5%, 95%	1.148, 17.524	0.001, 0.021	
	# of BLQ/ALQ Values	0/0	25/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	6.692, 4.787	0.006, 0.003	
	SD, SE	4.8008, 0.6789	0.0095, 0.0012	
	MEDIAN	5.297	0.003	
	MIN, MAX	0.050, 20.195	0.001, 0.046	
	5%, 95%	0.653, 16.414	0.001, 0.026	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438447

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 84 of 264)

Biomarker: Total 3-hydroxycotinine (nmol/mg Creatinine)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	33.556, 23.089	0.030, NA	
	SD, SE	24.2611, 3.4310	0.0509, 0.0063	
	MEDIAN	27.964	0.010	
	MIN, MAX	0.395, 95.647	0.000, 0.271	
	5%, 95%	1.925, 83.232	0.005, 0.114	
	# of BLQ/ALQ Values	0/0	23/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	35.235, 24.911	0.040, NA	
	SD, SE	25.6293, 3.6613	0.0811, 0.0101	
	MEDIAN	28.897	0.010	
	MIN, MAX	0.281, 104.185	0.000, 0.515	
	5%, 95%	2.617, 94.351	0.005, 0.140	
	# of BLQ/ALQ Values	0/0	15/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	36.028, 24.775	0.026, 0.015	
	SD, SE	27.6752, 4.0803	0.0415, 0.0051	
	MEDIAN	26.091	0.010	
	MIN, MAX	0.239, 121.199	0.005, 0.260	
	5%, 95%	5.973, 91.177	0.005, 0.109	
	# of BLQ/ALQ Values	0/0	25/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	34.818, 24.906	0.032, 0.017	
	SD, SE	24.9784, 3.5325	0.0493, 0.0061	
	MEDIAN	27.557	0.016	
	MIN, MAX	0.305, 105.075	0.003, 0.241	
	5%, 95%	3.399, 85.402	0.005, 0.135	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438448

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 85 of 264)

Biomarker: Total 3-hydroxycotinine ((µg/mg Creatinine)/cigarette per day) Analytical Lab: Harrogate			
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	0.457, 0.341	
	SD, SE	0.4171, 0.0590	
	MEDIAN	0.376	
	MIN, MAX	0.021, 2.536	
	5%, 95%	0.077, 1.054	
	# of BLQ/ALQ Values	0/0	
Week 2	N	49	
	MEAN, GEO MEAN	0.595, 0.386	
	SD, SE	0.9893, 0.1413	
	MEDIAN	0.377	
	MIN, MAX	0.018, 7.069	
	5%, 95%	0.139, 1.211	
	# of BLQ/ALQ Values	0/0	
Week 3	N	46	
	MEAN, GEO MEAN	0.511, 0.380	
	SD, SE	0.4645, 0.0685	
	MEDIAN	0.381	
	MIN, MAX	0.015, 2.859	
	5%, 95%	0.151, 1.165	
	# of BLQ/ALQ Values	0/0	
Overall*	N	50	
	MEAN, GEO MEAN	0.524, 0.384	
	SD, SE	0.5899, 0.0834	
	MEDIAN	0.406	
	MIN, MAX	0.019, 4.155	
	5%, 95%	0.163, 1.346	
			NA

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438449

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 86 of 264)

Biomarker: Total 3-hydroxycotinine ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	2.376, 1.774		
	SD, SE	2.1705, 0.3070		
	MEDIAN	1.956		
	MIN, MAX	0.107, 13.195		
	5%, 95%	0.401, 5.486		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	3.097, 2.010		
	SD, SE	5.1472, 0.7353		
	MEDIAN	1.964		
	MIN, MAX	0.094, 36.780		
	5%, 95%	0.725, 6.299		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	2.659, 1.975		
	SD, SE	2.4170, 0.3564		
	MEDIAN	1.981		
	MIN, MAX	0.080, 14.876		
	5%, 95%	0.786, 6.061		
	# of BLQ/ALQ Values	0/0		
Overall*	N	50		NA
	MEAN, GEO MEAN	2.726, 1.999		
	SD, SE	3.0691, 0.4340		
	MEDIAN	2.113		
	MIN, MAX	0.102, 21.617		
	5%, 95%	0.850, 7.002		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438450

Final Draft: 22 October 2003

Page 481 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 87 of 264)

Biomarker: Total 3-hydroxycotinine (ng/mL)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	4845.2, 3134.1	5.3, 2.4	
	SD, SE	4478.12, 633.30	12.40, 1.54	
	MEDIAN	3846.4	1.5	
	MIN, MAX	57.0, 26581.8	1.0, 96.1	
	5%, 95%	547.1, 12291.4	1.0, 18.0	
	# of BLQ/ALQ Values	0/0	23/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	5978.4, 4009.9	7.7, 2.8	
	SD, SE	4841.56, 691.65	22.20, 2.75	
	MEDIAN	4802.7	2.0	
	MIN, MAX	53.8, 23327.3	1.0, 169.4	
	5%, 95%	807.0, 16284.7	1.0, 26.2	
	# of BLQ/ALQ Values	0/0	15/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	5051.2, 3479.7	4.4, 2.2	
	SD, SE	4249.51, 626.56	9.19, 1.14	
	MEDIAN	4050.7	1.4	
	MIN, MAX	49.9, 23404.7	1.0, 69.1	
	5%, 95%	703.4, 12479.5	1.0, 15.6	
	# of BLQ/ALQ Values	0/0	25/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	5246.8, 3729.5	5.8, 2.7	
	SD, SE	3898.69, 551.36	11.54, 1.43	
	MEDIAN	4786.8	2.1	
	MIN, MAX	53.6, 18644.1	1.0, 66.3	
	5%, 95%	745.1, 11100.3	1.0, 18.6	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438451

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 88 of 264)

Biomarker: Total 3-hydroxycotinine (nmol/L)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	25209.6, 16307.0	27.8, 12.7	
	SD, SE	23299.65, 3295.07	64.53, 8.00	
	MEDIAN	20012.6	7.8	
	MIN, MAX	296.6, 138305.1	5.2, 500.0	
	5%, 95%	2846.6, 63952.2	5.2, 93.7	
	# of BLQ/ALQ Values	0/0	23/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	31105.5, 20863.4	40.2, 14.5	
	SD, SE	25190.66, 3598.67	115.52, 14.33	
	MEDIAN	24988.4	10.4	
	MIN, MAX	279.9, 121371.9	5.2, 881.4	
	5%, 95%	4198.8, 84729.3	5.2, 136.3	
	# of BLQ/ALQ Values	0/0	15/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	26281.4, 18105.1	22.7, 11.4	
	SD, SE	22110.22, 3259.97	47.79, 5.93	
	MEDIAN	21075.5	7.3	
	MIN, MAX	259.6, 121774.7	5.2, 359.5	
	5%, 95%	3659.8, 64930.8	5.2, 81.2	
	# of BLQ/ALQ Values	0/0	25/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	27299.0, 19404.3	30.2, 14.3	
	SD, SE	20284.91, 2868.72	60.02, 7.44	
	MEDIAN	24905.7	10.7	
	MIN, MAX	278.7, 97005.2	5.2, 344.8	
	5%, 95%	3876.6, 57754.9	5.2, 96.8	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438452

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 89 of 264)

Biomarker: Total 3-hydroxycotinine ((ng/mL)/cigarette per day)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	318.3, 240.8		
	SD, SE	225.62, 31.91		
	MEDIAN	247.1		
	MIN, MAX	19.0, 886.1		
	5%, 95%	59.0, 794.9		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	459.8, 323.5		
	SD, SE	434.21, 62.03		
	MEDIAN	361.8		
	MIN, MAX	17.9, 2304.5		
	5%, 95%	100.8, 1254.0		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	403.0, 277.4		
	SD, SE	467.53, 68.93		
	MEDIAN	294.0		
	MIN, MAX	16.6, 2993.5		
	5%, 95%	94.8, 1017.6		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	395.9, 297.1		
	SD, SE	328.26, 46.42		
	MEDIAN	305.0		
	MIN, MAX	17.8, 1912.2		
	5%, 95%	104.8, 924.4		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438453

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 90 of 264)

Biomarker: Total 3-hydroxycotinine ((nmol/L)/cigarette per day)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	1656.1, 1252.7		
	SD, SE	1173.92, 166.02		
	MEDIAN	1285.7		
	MIN, MAX	98.9, 4610.2		
	5%, 95%	306.7, 4135.8		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	2392.5, 1683.3		
	SD, SE	2259.19, 322.74		
	MEDIAN	1882.5		
	MIN, MAX	93.3, 11990.1		
	5%, 95%	524.4, 6524.6		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	2096.7, 1443.2		
	SD, SE	2432.56, 358.66		
	MEDIAN	1529.8		
	MIN, MAX	86.5, 15575.1		
	5%, 95%	493.0, 5294.6		
	# of BLQ/ALQ Values	0/0		
Overall*	N	50		NA
	MEAN, GEO MEAN	2060.0, 1545.7		
	SD, SE	1707.96, 241.54		
	MEDIAN	1586.8		
	MIN, MAX	92.9, 9949.3		
	5%, 95%	545.2, 4809.9		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438454

Final Draft: 22 October 2003

Page 485 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 91 of 264)

Biomarker: Total Cotinine (µg/24hr) Analytical Lab: Harrogate				
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	4878.376, 3421.217	5320, 2.894	
	SD, SE	3440.7648, 486.5976	8.2060, 1.0178	
	MEDIAN	4470.819	2.265	
	MIN, MAX	44.556, 17099.775	0.570, 46.593	
	5%, 95%	720.720, 10349.625	1.030, 23.940	
	# of BLQ/ALQ Values	0/0	33/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	5021.687, 3664.557	6388, 3.245	
	SD, SE	3238.0901, 462.5843	12.6004, 1.5629	
	MEDIAN	5068.690	2.740	
	MIN, MAX	25.650, 16352.593	0.625, 95.190	
	5%, 95%	735.694, 11710.980	0.915, 17.978	
	# of BLQ/ALQ Values	0/0	32/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	5092.021, 3687.215	4722, 2.969	
	SD, SE	3093.8123, 456.1577	7.0846, 0.8787	
	MEDIAN	5049.495	2.450	
	MIN, MAX	21.379, 13322.126	0.990, 43.940	
	5%, 95%	538.890, 10641.330	1.200, 14.945	
	# of BLQ/ALQ Values	0/0	39/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	4922.139, 3635.756	5476, 3.257	
	SD, SE	3018.0300, 426.8139	8.0065, 0.9931	
	MEDIAN	5080.985	2.658	
	MIN, MAX	30.578, 13142.481	0.967, 48.539	
	5%, 95%	834.401, 10962.570	1.181, 21.198	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438455

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 92 of 264)

Biomarker: Total Cotinine (nmol/24hr)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	27684.781, 19415.407	30.188, 16.426	
	SD, SE	19526.3404, 2761.4415	46.5690, 5.7762	
	MEDIAN	25371.898	12.854	
	MIN, MAX	252.855, 97041.223	3.235, 264.415	
	5%, 95%	4090.086, 58734.122	5.845, 135.860	
	# of BLQ/ALQ Values	0/0	33/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	28498.074, 20796.363	36.250, 18.415	
	SD, SE	18376.1613, 2625.1659	71.5075, 8.8694	
	MEDIAN	28764.816	15.550	
	MIN, MAX	145.564, 92800.965	3.547, 540.203	
	5%, 95%	4175.063, 66459.812	5.193, 102.025	
	# of BLQ/ALQ Values	0/0	32/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	28897.221, 20924.944	26.797, 16.847	
	SD, SE	17557.3848, 2588.6952	40.2052, 4.9868	
	MEDIAN	28655.882	13.904	
	MIN, MAX	121.326, 75603.065	5.618, 249.360	
	5%, 95%	3058.201, 60389.548	6.810, 84.813	
	# of BLQ/ALQ Values	0/0	39/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	27933.141, 20632.919	31.079, 18.485	
	SD, SE	17127.3203, 2422.1689	45.4372, 5.6358	
	MEDIAN	28834.590	15.082	
	MIN, MAX	173.248, 74583.582	5.486, 275.461	
	5%, 95%	4735.227, 62212.586	6.704, 120.299	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438456

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 93 of 264)

Biomarker: Total Cotinine ((µg/24hr)/cigarette per day)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	329.496, 262.807		
	SD, SE	255.9854, 36.2018		
	MEDIAN	265.098		
	MIN, MAX	14.852, 1709.978		
	5%, 95%	67.906, 733.236		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	387.177, 295.663		
	SD, SE	348.4011, 49.7716		
	MEDIAN	285.478		
	MIN, MAX	8.550, 1900.378		
	5%, 95%	148.824, 1113.879		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	366.558, 293.920		
	SD, SE	216.7281, 31.9548		
	MEDIAN	305.509		
	MIN, MAX	7.126, 918.949		
	5%, 95%	104.652, 645.604		
	# of BLQ/ALQ Values	0/0		
Overall*	N	50		NA
	MEAN, GEO MEAN	359.150, 292.773		
	SD, SE	239.4210, 33.8592		
	MEDIAN	280.147		
	MIN, MAX	10.176, 1378.107		
	5%, 95%	136.146, 735.186		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438457

Final Draft: 22 October 2003

Page 488 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 94 of 264)

Biomarker: Total Cotinine ((nmol/24hr)/cigarette per day)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	1869.889, 1491.430		
	SD, SE	1452.7166, 205.4451		
	MEDIAN	1504.427		
	MIN, MAX	84.285, 9704.122		
	5%, 95%	385.369, 4161.114		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	2197.228, 1677.887		
	SD, SE	1977.1759, 282.4537		
	MEDIAN	1620.085		
	MIN, MAX	48.521, 10784.643		
	5%, 95%	844.576, 6321.264		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	2080.214, 1667.997		
	SD, SE	1229.9317, 181.3435		
	MEDIAN	1733.765		
	MIN, MAX	40.442, 5215.035		
	5%, 95%	593.900, 4798.800		
	# of BLQ/ALQ Values	0/0		
Overall*	N	50		NA
	MEAN, GEO MEAN	2038.178, 1661.487		
	SD, SE	1358.7135, 192.1511		
	MEDIAN	1589.832		
	MIN, MAX	57.749, 7820.754		
	5%, 95%	772.628, 4172.178		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438458

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 95 of 264)

Biomarker: Total Cotinine (µg/mg Creatinine)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	3.957, 2.835	0.004, NA	
	SD, SE	2.4437, 0.3456	0.0057, 0.0007	
	MEDIAN	3.861	0.002	
	MIN, MAX	0.042, 10.371	0.000, 0.033	
	5%, 95%	0.473, 8.403	0.001, 0.015	
	# of BLQ/ALQ Values	0/0	33/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	3.842, 2.829	0.005, NA	
	SD, SE	2.5305, 0.3615	0.0114, 0.0014	
	MEDIAN	3.699	0.002	
	MIN, MAX	0.029, 12.831	0.000, 0.091	
	5%, 95%	0.636, 8.239	0.001, 0.014	
	# of BLQ/ALQ Values	0/0	32/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	4.042, 2.957	0.003, 0.002	
	SD, SE	2.6149, 0.3855	0.0044, 0.0005	
	MEDIAN	3.681	0.002	
	MIN, MAX	0.019, 11.859	0.001, 0.025	
	5%, 95%	0.832, 9.415	0.001, 0.008	
	# of BLQ/ALQ Values	0/0	39/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	3.950, 2.935	0.004, 0.002	
	SD, SE	2.4396, 0.3450	0.0061, 0.0008	
	MEDIAN	3.804	0.002	
	MIN, MAX	0.030, 10.694	0.001, 0.042	
	5%, 95%	0.733, 8.810	0.001, 0.015	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438459

Final Draft: 22 October 2003

Page 490 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 96 of 264)

Biomarker: Total Cotinine (nmol/mg Creatinine)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	22.456, 16.086	0.021, NA	
	SD, SE	13.8680, 1.9612	0.0321, 0.0040	
	MEDIAN	21.912	0.011	
	MIN, MAX	0.238, 58.855	0.000, 0.187	
	5%, 95%	2.684, 47.687	0.006, 0.085	
	# of BLQ/ALQ Values	0/0	33/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	21.801, 16.055	0.028, NA	
	SD, SE	14.3604, 2.0515	0.0647, 0.0080	
	MEDIAN	20.992	0.011	
	MIN, MAX	0.165, 72.816	0.000, 0.516	
	5%, 95%	3.609, 46.756	0.006, 0.079	
	# of BLQ/ALQ Values	0/0	32/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	22.940, 16.783	0.019, 0.012	
	SD, SE	14.8394, 2.1880	0.0252, 0.0031	
	MEDIAN	20.887	0.011	
	MIN, MAX	0.108, 67.300	0.006, 0.142	
	5%, 95%	4.722, 53.430	0.006, 0.045	
	# of BLQ/ALQ Values	0/0	39/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	22.417, 16.655	0.023, 0.014	
	SD, SE	13.8448, 1.9579	0.0347, 0.0043	
	MEDIAN	21.585	0.011	
	MIN, MAX	0.170, 60.690	0.004, 0.240	
	5%, 95%	4.162, 49.999	0.006, 0.085	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438460

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 97 of 264)

Biomarker: Total Cotinine ((µg/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	0.289, 0.218	
	SD, SE	0.2716, 0.0384	
	MEDIAN	0.205	
	MIN, MAX	0.014, 1.681	
	5%, 95%	0.094, 0.690	
	# of BLQ/ALQ Values	0/0	
Week 2	N	49	
	MEAN, GEO MEAN	0.339, 0.228	
	SD, SE	0.5357, 0.0765	
	MEDIAN	0.198	
	MIN, MAX	0.010, 3.761	
	5%, 95%	0.094, 0.716	
	# of BLQ/ALQ Values	0/0	
Week 3	N	46	
	MEAN, GEO MEAN	0.308, 0.235	
	SD, SE	0.2648, 0.0390	
	MEDIAN	0.232	
	MIN, MAX	0.006, 1.482	
	5%, 95%	0.095, 0.831	
	# of BLQ/ALQ Values	0/0	
Overall*	N	50	
	MEAN, GEO MEAN	0.314, 0.237	
	SD, SE	0.3292, 0.0466	
	MEDIAN	0.221	
	MIN, MAX	0.010, 2.177	
	5%, 95%	0.104, 0.584	
			NA

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438461

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 98 of 264)

Biomarker: Total Cotinine ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	1.637, 1.236		
	SD, SE	1.5410, 0.2179		
	MEDIAN	1.164		
	MIN, MAX	0.079, 9.537		
	5%, 95%	0.536, 3.918		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	1.923, 1.295		
	SD, SE	3.0402, 0.4343		
	MEDIAN	1.125		
	MIN, MAX	0.055, 21.344		
	5%, 95%	0.531, 4.063		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	1.746, 1.338		
	SD, SE	1.5031, 0.2216		
	MEDIAN	1.317		
	MIN, MAX	0.036, 8.413		
	5%, 95%	0.542, 4.718		
	# of BLQ/ALQ Values	0/0		
Overall*	N	50		NA
	MEAN, GEO MEAN	1.779, 1.343		
	SD, SE	1.8683, 0.2642		
	MEDIAN	1.255		
	MIN, MAX	0.057, 12.354		
	5%, 95%	0.588, 3.315		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438462

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 99 of 264)

Biomarker: Total Cotinine (ng/mL) Analytical Lab: Harrogate				
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	3187.2, 2002.0	3.0, 1.8	
	SD, SE	2909.78, 411.50	5.10, 0.63	
	MEDIAN	2020.8	1.0	
	MIN, MAX	31.6, 12610.5	1.0, 35.5	
	5%, 95%	348.7, 10113.6	1.0, 10.7	
	# of BLQ/ALQ Values	0/0	33/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	3644.7, 2368.7	3.4, 1.9	
	SD, SE	3403.71, 486.24	5.70, 0.71	
	MEDIAN	2690.9	1.2	
	MIN, MAX	28.5, 18373.7	1.0, 33.4	
	5%, 95%	503.9, 9222.8	1.0, 14.1	
	# of BLQ/ALQ Values	0/0	32/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	3056.7, 2160.4	2.5, 1.6	
	SD, SE	2083.46, 307.19	4.43, 0.55	
	MEDIAN	2403.3	1.0	
	MIN, MAX	20.4, 7919.1	1.0, 33.8	
	5%, 95%	390.5, 6761.2	1.0, 6.2	
	# of BLQ/ALQ Values	0/0	39/0	
Overall [*]	N	50	65	<.0001
	MEAN, GEO MEAN	3256.3, 2246.5	3.0, 1.9	
	SD, SE	2553.08, 361.06	4.30, 0.53	
	MEDIAN	2699.1	1.2	
	MIN, MAX	26.8, 12581.8	1.0, 27.1	
	5%, 95%	464.3, 7394.7	1.0, 11.3	

^a P-value from Wilcoxon rank-sum test.

^{*} Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438463

Final Draft: 22 October 2003

Page 494 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 100 of 264)

Biomarker: Total Cotinine (nmol/L) Analytical Lab: Harrogate				
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	18087.2, 11361.6	17.3, 10.1	
	SD, SE	16513.00, 2335.29	28.95, 3.59	
	MEDIAN	11468.1	5.7	
	MIN, MAX	179.3, 71564.6	5.7, 201.5	
	5%, 95%	1978.9, 57394.7	5.7, 60.7	
	# of BLQ/ALQ Values	0/0	33/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	20683.9, 13442.5	19.4, 10.8	
	SD, SE	19316.06, 2759.44	32.33, 4.01	
	MEDIAN	15270.9	6.8	
	MIN, MAX	161.7, 104270.7	5.7, 189.5	
	5%, 95%	2859.6, 52339.4	5.7, 80.0	
	# of BLQ/ALQ Values	0/0	32/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	17347.0, 12260.6	14.3, 9.1	
	SD, SE	11823.64, 1743.30	25.13, 3.12	
	MEDIAN	13638.4	5.7	
	MIN, MAX	115.8, 44940.9	5.7, 191.8	
	5%, 95%	2216.1, 38369.8	5.7, 35.2	
	# of BLQ/ALQ Values	0/0	39/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	18479.7, 12749.4	17.0, 10.7	
	SD, SE	14488.77, 2049.02	24.40, 3.03	
	MEDIAN	15317.2	6.8	
	MIN, MAX	152.3, 71401.7	5.7, 153.6	
	5%, 95%	2634.7, 41965.1	5.7, 64.0	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics).

PM3006438464

Final Draft: 22 October 2003

Page 495 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 101 of 264)

Biomarker: Total Cotinine ((ng/mL)/cigarette per day)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	208.8, 153.8		
	SD, SE	171.02, 24.19		
	MEDIAN	142.9		
	MIN, MAX	10.5, 842.8		
	5%, 95%	56.1, 573.2		
Week 2	# of BLQ/ALQ Values	0/0		NA
	N	49		
	MEAN, GEO MEAN	268.7, 191.1		
	SD, SE	242.85, 34.69		
	MEDIAN	191.9		
	MIN, MAX	9.5, 1226.1		
Week 3	5%, 95%	57.9, 918.7		NA
	# of BLQ/ALQ Values	0/0		
	N	46		
	MEAN, GEO MEAN	244.5, 172.2		
	SD, SE	227.66, 33.57		
	MEDIAN	160.0		
Overall*	MIN, MAX	6.8, 1140.3		NA
	5%, 95%	61.5, 824.2		
	# of BLQ/ALQ Values	0/0		
	N	50		
	MEAN, GEO MEAN	239.5, 179.8		
	SD, SE	188.32, 26.63		
	MEDIAN	180.5		
	MIN, MAX	8.9, 885.7		
	5%, 95%	58.7, 647.5		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438465

Final Draft: 22 October 2003

Page 496 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14 2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 102 of 264)

Biomarker: Total Cotinine ((nmol/L)/cigarette per day)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	1184.7, 872.8		
	SD, SE	970.51, 137.25		
	MEDIAN	810.6		
	MIN, MAX	59.8, 4782.9		
	5%, 95%	318.3, 3252.9		
Week 2	# of BLQ/ALQ Values	0/0		NA
	N	49		
	MEAN, GEO MEAN	1524.6, 1084.6		
	SD, SE	1378.13, 196.88		
	MEDIAN	1088.8		
	MIN, MAX	53.9, 6957.9		
Week 3	5%, 95%	328.4, 5213.5		NA
	# of BLQ/ALQ Values	0/0		
	N	46		
	MEAN, GEO MEAN	1387.3, 977.3		
	SD, SE	1291.97, 190.49		
	MEDIAN	907.7		
Overall*	MIN, MAX	38.6, 6471.0		NA
	5%, 95%	349.2, 4677.2		
	# of BLQ/ALQ Values	0/0		
	N	50		
	MEAN, GEO MEAN	1359.4, 1020.2		
	SD, SE	1068.71, 151.14		
Overall*	MEDIAN	1024.4		NA
	MIN, MAX	50.8, 5026.3		
	5%, 95%	333.1, 3674.8		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438466

Final Draft: 22 October 2003

Page 497 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 103 of 264)

Biomarker: Total Nicotine (µg/24hr) Analytical Lab: Harrogate				
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	2388.232, 1566.128	5.178, 2.339	
	SD, SE	1770.0820, 250.3274	13.2947, 1.6490	
	MEDIAN	2032.229	1.980	
	MIN, MAX	22.137, 6337.875	0.530, 88.160	
	5%, 95%	152.361, 5830.265	0.800, 17.248	
	# of BLQ/ALQ Values	0/0	43/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	2506.711, 1693.852	8.023, 2.287	
	SD, SE	1845.8417, 263.6917	42.9602, 5.3286	
	MEDIAN	2099.049	2.025	
	MIN, MAX	10.710, 9552.459	0.625, 348.555	
	5%, 95%	192.780, 5810.675	0.815, 7.128	
	# of BLQ/ALQ Values	0/0	50/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	2737.439, 1824.195	2.764, 2.222	
	SD, SE	1983.6441, 292.4724	2.6887, 0.3335	
	MEDIAN	2327.148	2.064	
	MIN, MAX	10.061, 7734.320	0.750, 19.760	
	5%, 95%	288.769, 7314.615	0.990, 7.224	
	# of BLQ/ALQ Values	0/0	51/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	2497.610, 1731.917	5.322, 2.469	
	SD, SE	1659.2686, 234.6560	17.3113, 2.1472	
	MEDIAN	2046.091	2.143	
	MIN, MAX	14.303, 6909.321	0.967, 138.186	
	5%, 95%	172.571, 5294.825	1.057, 11.448	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438467

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 104 of 264)

Biomarker: Total Nicotine (nmol/24hr)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	14723.452, 9655.183	31.925, 14.418	
	SD, SE	10912.5555, 1543.2684	81.9620, 10.1661	
	MEDIAN	12528.692	12.207	
	MIN, MAX	136.475, 39072.999	3.267, 543.506	
	5%, 95%	939.306, 35943.584	4.932, 106.334	
	# of BLQ/ALQ Values	0/0	43/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	15453.873, 10442.598	49.460, 14.099	
	SD, SE	11379.6144, 1625.6592	264.8496, 32.8505	
	MEDIAN	12940.637	12.484	
	MIN, MAX	66.027, 58890.910	3.853, 2148.842	
	5%, 95%	1188.489, 35822.811	5.024, 43.944	
	# of BLQ/ALQ Values	0/0	50/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	16876.314, 11246.162	17.039, 13.700	
	SD, SE	12229.1660, 1803.0921	16.5761, 2.0560	
	MEDIAN	14346.868	12.725	
	MIN, MAX	62.026, 47682.083	4.624, 121.820	
	5%, 95%	1780.261, 45094.601	6.103, 44.536	
	# of BLQ/ALQ Values	0/0	51/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	15397.769, 10677.263	32.808, 15.224	
	SD, SE	10229.3910, 1446.6543	106.7245, 13.2375	
	MEDIAN	12614.151	13.214	
	MIN, MAX	88.176, 42595.964	5.960, 851.919	
	5%, 95%	1063.898, 32642.594	6.514, 70.579	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438468

Final Draft: 22 October 2003

Page 499 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 105 of 264)

Biomarker: Total Nicotine ((pg/24hr)/cigarette per day)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	158.841, 120.305		
	SD, SE	121.2265, 17.1440		
	MEDIAN	141.516		
	MIN, MAX	7.379, 621.350		
	5%, 95%	28.884, 416.448		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	205.584, 136.663		
	SD, SE	277.5279, 39.6468		
	MEDIAN	139.937		
	MIN, MAX	3.570, 1882.398		
	5%, 95%	46.464, 569.535		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	185.832, 145.413		
	SD, SE	113.3303, 16.7096		
	MEDIAN	170.006		
	MIN, MAX	3.354, 543.137		
	5%, 95%	41.253, 411.403		
	# of BLQ/ALQ Values	0/0		
Overall**	N	50		NA
	MEAN, GEO MEAN	180.458, 141.547		
	SD, SE	143.6449, 20.3145		
	MEDIAN	143.212		
	MIN, MAX	4.768, 921.368		
	5%, 95%	53.275, 367.479		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

** Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438469

Final Draft: 22 October 2003

Page 500 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 106 of 264)

Biomarker: Total Nicotine ((nmol/24hr)/cigarette per day)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	979.256, 741.681		
	SD, SE	747.3612, 105.6928		
	MEDIAN	872.441		
	MIN, MAX	45.492, 3830.625		
	5%, 95%	178.070, 2567.399		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	1267.426, 842.527		
	SD, SE	1710.9592, 244.4227		
	MEDIAN	862.709		
	MIN, MAX	22.009, 11604.981		
	5%, 95%	286.451, 3511.183		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	1145.652, 896.469		
	SD, SE	698.6815, 103.0150		
	MEDIAN	1048.089		
	MIN, MAX	20.675, 3348.442		
	5%, 95%	254.323, 2536.296		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	1112.524, 872.634		
	SD, SE	885.5711, 125.2387		
	MEDIAN	882.901		
	MIN, MAX	29.392, 5680.232		
	5%, 95%	328.440, 2265.509		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438470

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 107 of 264)

Biomarker: Total Nicotine (µg/mg Creatinine)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	2.020, 1.298	0.003, NA	
	SD, SE	1.7387, 0.2459	0.0076, 0.0009	
	MEDIAN	1.727	0.002	
	MIN, MAX	0.021, 9.353	0.000, 0.044	
	5%, 95%	0.100, 5.254	0.000, 0.011	
	# of BLQ/ALQ Values	0/0	43/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	1.974, 1.307	0.007, NA	
	SD, SE	1.6781, 0.2397	0.0411, 0.0051	
	MEDIAN	1.686	0.001	
	MIN, MAX	0.012, 7.495	0.000, 0.333	
	5%, 95%	0.144, 6.431	0.000, 0.004	
	# of BLQ/ALQ Values	0/0	50/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	2.100, 1.463	0.002, NA	
	SD, SE	1.3912, 0.2051	0.0015, 0.0002	
	MEDIAN	2.056	0.002	
	MIN, MAX	0.009, 5.794	0.000, 0.011	
	5%, 95%	0.200, 4.966	0.000, 0.004	
	# of BLQ/ALQ Values	0/0	51/0	
Overall [†]	N	50	65	<.0001
	MEAN, GEO MEAN	2.027, 1.398	0.004, NA	
	SD, SE	1.4655, 0.2073	0.0155, 0.0019	
	MEDIAN	1.811	0.002	
	MIN, MAX	0.014, 6.341	0.000, 0.126	
	5%, 95%	0.156, 5.620	0.000, 0.008	

* P-value from Wilcoxon rank-sum test.

[†] Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438471

Final Draft: 22 October 2003

Page 502 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 108 of 264)

Biomarker: Total Nicotine (nmol/mg Creatinine) Analytical Lab: Harrogate				
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	12.456, 8.001	0.021, NA	
	SD, SE	10.7192, 1.5159	0.0466, 0.0058	
	MEDIAN	10.644	0.012	
	MIN, MAX	0.129, 57.661	0.000, 0.271	
	5%, 95%	0.617, 32.391	0.000, 0.068	
	# of BLQ/ALQ Values	0/0	43/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	12.170, 8.060	0.044, NA	
	SD, SE	10.3455, 1.4779	0.2535, 0.0314	
	MEDIAN	10.394	0.006	
	MIN, MAX	0.074, 46.207	0.000, 2.053	
	5%, 95%	0.888, 39.647	0.000, 0.025	
	# of BLQ/ALQ Values	0/0	50/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	12.945, 9.019	0.012, NA	
	SD, SE	8.5770, 1.2646	0.0100, 0.0012	
	MEDIAN	12.673	0.012	
	MIN, MAX	0.055, 35.720	0.000, 0.068	
	5%, 95%	1.233, 30.615	0.000, 0.025	
	# of BLQ/ALQ Values	0/0	51/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	12.496, 8.617	0.026, 0.011	
	SD, SE	9.0349, 1.2777	0.0960, 0.0119	
	MEDIAN	11.165	0.010	
	MIN, MAX	0.086, 39.094	0.002, 0.779	
	5%, 95%	0.960, 34.649	0.002, 0.049	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438472

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 109 of 264)

Biomarker: Total Nicotine ((µg/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	0.154, 0.100		
	SD, SE	0.2594, 0.0367		
	MEDIAN	0.095		
	MIN, MAX	0.007, 1.871		
	5%, 95%	0.028, 0.288		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	0.202, 0.105		
	SD, SE	0.5228, 0.0747		
	MEDIAN	0.107		
	MIN, MAX	0.004, 3.726		
	5%, 95%	0.033, 0.375		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	0.149, 0.117		
	SD, SE	0.1015, 0.0150		
	MEDIAN	0.125		
	MIN, MAX	0.003, 0.484		
	5%, 95%	0.029, 0.393		
	# of BLQ/ALQ Values	0/0		
Overall [*]	N	50		NA
	MEAN, GEO MEAN	0.168, 0.115		
	SD, SE	0.2771, 0.0392		
	MEDIAN	0.110		
	MIN, MAX	0.005, 2.014		
	5%, 95%	0.036, 0.296		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^{*} Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438473

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 110 of 264)

Biomarker: Total Nicotine ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	0.950, 0.615		
	SD, SE	1.5985, 0.2261		
	MEDIAN	0.583		
	MIN, MAX	0.043, 11.532		
	5%, 95%	0.175, 1.776		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	1.245, 0.650		
	SD, SE	3.2226, 0.4604		
	MEDIAN	0.662		
	MIN, MAX	0.025, 22.968		
	5%, 95%	0.205, 2.310		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	0.921, 0.719		
	SD, SE	0.6259, 0.0923		
	MEDIAN	0.767		
	MIN, MAX	0.018, 2.983		
	5%, 95%	0.176, 2.422		
	# of BLQ/ALQ Values	0/0		
Overall*	N	50		NA
	MEAN, GEO MEAN	1.035, 0.705		
	SD, SE	1.7079, 0.2415		
	MEDIAN	0.682		
	MIN, MAX	0.029, 12.412		
	5%, 95%	0.220, 1.824		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438474

Final Draft: 22 October 2003

Page 505 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 111 of 264)

Biomarker: Total Nicotine (ng/mL) Analytical Lab: Harrogate				
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	1612.6, 916.5	2.4, 1.4	
	SD, SE	1653.11, 233.78	4.50, 0.56	
	MEDIAN	1000.4	1.0	
	MIN, MAX	15.7, 8096.4	1.0, 23.2	
	5%, 95%	88.4, 5070.3	1.0, 8.8	
	# of BLQ/ALQ Values	0/0	43/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	1794.7, 1094.9	3.3, 1.3	
	SD, SE	1855.53, 265.08	15.04, 1.87	
	MEDIAN	1304.2	1.0	
	MIN, MAX	11.9, 10733.1	1.0, 122.3	
	5%, 95%	151.2, 5120.6	1.0, 5.1	
	# of BLQ/ALQ Values	0/0	50/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	1611.1, 1058.8	1.5, 1.2	
	SD, SE	1234.16, 181.97	1.87, 0.23	
	MEDIAN	1301.9	1.0	
	MIN, MAX	9.6, 4831.6	1.0, 15.2	
	5%, 95%	253.9, 3911.0	1.0, 2.1	
	# of BLQ/ALQ Values	0/0	51/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	1646.9, 1057.4	2.4, 1.4	
	SD, SE	1449.86, 205.04	6.13, 0.76	
	MEDIAN	1216.9	1.0	
	MIN, MAX	12.4, 7887.0	1.0, 48.6	
	5%, 95%	163.9, 3865.6	1.0, 4.5	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234) will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438475

Final Draft: 22 October 2003

Page 506 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 112 of 264)

Biomarker: Total Nicotine (nmol/L) Analytical Lab: Harrogate				P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	9941.7, 5650.1	15.0, 8.9	
	SD, SE	10191.41, 1441.28	27.75, 3.44	
	MEDIAN	6167.2	6.2	
	MIN, MAX	96.8, 49914.3	6.2, 143.0	
	5%, 95%	545.0, 31258.4	6.2, 54.3	
	# of BLQ/ALQ Values	0/0	43/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	11064.6, 6750.1	20.6, 8.3	
	SD, SE	11439.34, 1634.19	92.70, 11.50	
	MEDIAN	8040.4	6.2	
	MIN, MAX	73.4, 66169.6	6.2, 754.0	
	5%, 95%	932.1, 31568.5	6.2, 31.4	
	# of BLQ/ALQ Values	0/0	50/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	9932.6, 6589.5	9.0, 7.4	
	SD, SE	7608.62, 1121.83	11.51, 1.43	
	MEDIAN	8025.9	6.2	
	MIN, MAX	59.2, 29786.8	6.2, 93.7	
	5%, 95%	1565.3, 24111.3	6.2, 12.9	
	# of BLQ/ALQ Values	0/0	51/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	10152.9, 6518.8	14.8, 8.7	
	SD, SE	8938.40, 1264.08	37.79, 4.69	
	MEDIAN	7502.2	6.2	
	MIN, MAX	76.5, 48623.6	6.2, 299.8	
	5%, 95%	1010.2, 23831.4	6.2, 28.0	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438476

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 113 of 264)

Biomarker: Total Nicotine ((ng/mL)/cigarette per day)		Analytical Lab: Harrogate	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	104.0, 70.4	
	SD, SE	96.79, 13.69	
	MEDIAN	75.1	
	MIN, MAX	5.2, 458.8	
	5%, 95%	19.4, 323.6	
	# of BLQ/ALQ Values	0/0	
Week 2	N	49	
	MEAN, GEO MEAN	141.4, 88.3	
	SD, SE	190.40, 27.20	
	MEDIAN	83.4	
	MIN, MAX	4.0, 1214.5	
	5%, 95%	24.4, 403.2	
	# of BLQ/ALQ Values	0/0	
Week 3	N	46	
	MEAN, GEO MEAN	119.8, 85.2	
	SD, SE	99.86, 14.72	
	MEDIAN	87.0	
	MIN, MAX	3.2, 464.9	
	5%, 95%	22.4, 322.1	
	# of BLQ/ALQ Values	0/0	
Overall*	N	50	
	MEAN, GEO MEAN	119.8, 85.9	
	SD, SE	114.41, 16.18	
	MEDIAN	80.5	
	MIN, MAX	4.1, 667.7	
	5%, 95%	28.7, 325.3	
			NA

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438477

Final Draft: 22 October 2003

Page 508 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 114 of 264)

Biomarker: Total Nicotine ((nmol/L)/cigarette per day)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	641.2, 434.0		
	SD, SE	596.70, 84.39		
	MEDIAN	463.0		
	MIN, MAX	32.3, 2889.8		
	5%, 95%	119.9, 1995.1		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	871.9, 544.6		
	SD, SE	1173.74, 167.68		
	MEDIAN	514.2		
	MIN, MAX	24.5, 7487.1		
	5%, 95%	150.5, 2485.9		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	738.5, 525.3		
	SD, SE	615.68, 90.78		
	MEDIAN	535.8		
	MIN, MAX	19.7, 2866.2		
	5%, 95%	137.9, 1985.8		
	# of BLQ/ALQ Values	0/0		
Overall*	N	50		NA
	MEAN, GEO MEAN	738.5, 529.5		
	SD, SE	705.29, 99.74		
	MEDIAN	496.1		
	MIN, MAX	25.5, 4116.1		
	5%, 95%	176.9, 2005.1		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438478

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 115 of 264)

Biomarker: Trans-3-hydroxycotinine (pg/24hr)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	5745.431, 3951.124	6.964, 3.581	
	SD, SE	4337.8610, 613.4662	11.5984, 1.4386	
	MEDIAN	5379.732	2.800	
	MIN, MAX	42.441, 20367.215	0.855, 67.936	
	5%, 95%	645.000, 15778.245	1.030, 30.820	
	# of BLQ/ALQ Values	0/0	22/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	6615.884, 4719.000	9.250, 4.155	
	SD, SE	4263.6442, 609.0920	20.6533, 2.5617	
	MEDIAN	6368.085	2.910	
	MIN, MAX	24.210, 18154.368	0.750, 152.550	
	5%, 95%	722.866, 15032.830	1.023, 31.960	
	# of BLQ/ALQ Values	0/0	17/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	6170.891, 4344.157	6.512, 3.646	
	SD, SE	4218.9830, 622.0551	11.2227, 1.3920	
	MEDIAN	5068.953	2.890	
	MIN, MAX	21.379, 15121.480	0.990, 72.800	
	5%, 95%	976.686, 14222.565	1.300, 31.610	
	# of BLQ/ALQ Values	0/0	30/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	6093.854, 4444.837	7.576, 4.132	
	SD, SE	3968.4962, 561.2301	12.7435, 1.5806	
	MEDIAN	5310.133	3.182	
	MIN, MAX	29.343, 17222.174	1.038, 76.940	
	5%, 95%	696.229, 12433.240	1.303, 33.167	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438479

Final Draft: 22 October 2003

Page 510 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 116 of 264)

Biomarker: Trans-3-hydroxycotinine (nmol/24hr) Analytical Lab: Harrogate				
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	29893.480, 20557.701	36.235, 18.631	
	SD, SE	22569.8906, 3191.8645	60.3466, 7.4851	
	MEDIAN	27990.743	14.568	
	MIN, MAX	220.821, 105970.620	4.449, 353.471	
	5%, 95%	3355.935, 82094.209	5.359, 160.356	
	# of BLQ/ALQ Values	0/0	22/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	34422.443, 24552.957	48.129, 21.619	
	SD, SE	22183.7406, 3169.1058	107.4591, 13.3287	
	MEDIAN	33133.146	15.141	
	MIN, MAX	125.965, 94457.177	3.902, 793.718	
	5%, 95%	3761.072, 78215.814	5.323, 166.288	
	# of BLQ/ALQ Values	0/0	17/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	32107.148, 22602.652	33.883, 18.972	
	SD, SE	21951.3688, 3236.5528	58.3918, 7.2426	
	MEDIAN	26373.760	15.037	
	MIN, MAX	111.233, 78677.060	5.151, 378.778	
	5%, 95%	5081.697, 74000.006	6.764, 164.467	
	# of BLQ/ALQ Values	0/0	30/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	31706.321, 23126.495	39.416, 21.501	
	SD, SE	20648.0857, 2920.0803	66.3047, 8.2241	
	MEDIAN	27628.619	16.556	
	MIN, MAX	152.674, 89606.973	5.402, 400.319	
	5%, 95%	3622.478, 64690.148	6.778, 172.570	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438480

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 117 of 264)

Biomarker: Trans-3-hydroxycotinine ((µg/24hr)/cigarette per day)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	385.100, 303.513		
	SD, SE	266.5916, 37.7017		
	MEDIAN	325.512		
	MIN, MAX	14.147, 1577.825		
	5%, 95%	71.775, 899.285		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	506.178, 380.737		
	SD, SE	418.8634, 59.8376		
	MEDIAN	400.405		
	MIN, MAX	8.070, 2529.445		
	5%, 95%	164.300, 1157.695		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	436.853, 346.287		
	SD, SE	270.9947, 39.9560		
	MEDIAN	371.128		
	MIN, MAX	7.126, 1230.107		
	5%, 95%	159.486, 1036.347		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	442.816, 355.555		
	SD, SE	277.0733, 39.1841		
	MEDIAN	377.916		
	MIN, MAX	9.781, 1385.359		
	5%, 95%	148.070, 1006.597		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438481

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 118 of 264)

Biomarker: Trans-3-hydroxycotinine (nmol/24hr)/cigarette per day		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	2003.674, 1579.178		
	SD, SE	1387.0757, 196.1621		
	MEDIAN	1693.636		
	MIN, MAX	73.607, 8209.421		
	5%, 95%	373.446, 4678.980		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	2633.642, 1980.976		
	SD, SE	2179.3464, 311.3352		
	MEDIAN	2083.307		
	MIN, MAX	41.988, 13160.703		
	5%, 95%	854.853, 6023.487		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	2272.944, 1801.733		
	SD, SE	1409.9852, 207.8910		
	MEDIAN	1930.976		
	MIN, MAX	37.078, 6400.244		
	5%, 95%	829.805, 5392.114		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	2303.971, 1849.953		
	SD, SE	1441.6122, 203.8748		
	MEDIAN	1966.297		
	MIN, MAX	50.891, 7208.023		
	5%, 95%	770.409, 5237.322		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438482

Final Draft: 22 October 2003

Page 513 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 119 of 264)

Biomarker: Trans-3-hydroxycotinine (µg/mg Creatinine)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	4.766, 3.274	0.005, NA	
	SD, SE	3.4639, 0.4899	0.0080, 0.0010	
	MEDIAN	4.258	0.002	
	MIN, MAX	0.040, 14.351	0.000, 0.042	
	5%, 95%	0.300, 12.478	0.001, 0.019	
	# of BLQ/ALQ Values	0/0	22/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	5.168, 3.642	0.006, NA	
	SD, SE	3.6621, 0.5232	0.0123, 0.0015	
	MEDIAN	4.126	0.002	
	MIN, MAX	0.027, 15.297	0.000, 0.079	
	5%, 95%	0.400, 12.899	0.001, 0.019	
	# of BLQ/ALQ Values	0/0	17/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	5.034, 3.484	0.004, 0.003	
	SD, SE	3.6689, 0.5410	0.0062, 0.0008	
	MEDIAN	3.689	0.002	
	MIN, MAX	0.019, 15.542	0.001, 0.041	
	5%, 95%	0.770, 11.642	0.001, 0.017	
	# of BLQ/ALQ Values	0/0	30/0	
Overall [*]	N	50	65	<.0001
	MEAN, GEO MEAN	4.971, 3.566	0.005, 0.003	
	SD, SE	3.4521, 0.4882	0.0075, 0.0009	
	MEDIAN	4.113	0.002	
	MIN, MAX	0.029, 14.264	0.001, 0.037	
	5%, 95%	0.497, 12.705	0.001, 0.019	

^a P-value from Wilcoxon rank-sum test.

^{*} Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438483

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 120 of 264)

Biomarker: Trans-3-hydroxycotinine (nmol/mg Creatinine) Analytical Lab: Harrogate				P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	24.797, 17.032	0.026, NA	
	SD, SE	18.0226, 2.5488	0.0418, 0.0052	
	MEDIAN	22.155	0.010	
	MIN, MAX	0.208, 74.668	0.000, 0.219	
	5%, 95%	1.561, 64.923	0.005, 0.099	
	# of BLQ/ALQ Values	0/0	22/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	26.891, 18.948	0.032, NA	
	SD, SE	19.0536, 2.7219	0.0640, 0.0079	
	MEDIAN	21.468	0.010	
	MIN, MAX	0.140, 79.590	0.000, 0.411	
	5%, 95%	2.081, 67.113	0.005, 0.099	
	# of BLQ/ALQ Values	0/0	17/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	26.191, 18.128	0.022, 0.013	
	SD, SE	19.0893, 2.8146	0.0325, 0.0040	
	MEDIAN	19.194	0.010	
	MIN, MAX	0.099, 80.865	0.005, 0.213	
	5%, 95%	4.006, 60.573	0.005, 0.088	
	# of BLQ/ALQ Values	0/0	30/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	25.862, 18.548	0.027, 0.015	
	SD, SE	17.9615, 2.5401	0.0389, 0.0048	
	MEDIAN	21.398	0.012	
	MIN, MAX	0.149, 74.215	0.003, 0.194	
	5%, 95%	2.586, 66.106	0.005, 0.099	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438484

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 121 of 264)

Biomarker: Trans-3-hydroxycotinine ((µg/mg Creatinine)/cigarette per day) Analytical Lab: Harrogate				
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50		NA
	MEAN, GEO MEAN	0.340, 0.251		
	SD, SE	0.3073, 0.0435		
	MEDIAN	0.266		
	MIN, MAX	0.013, 1.777		
	5%, 95%	0.060, 0.957		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	0.450, 0.294		
	SD, SE	0.7038, 0.1005		
	MEDIAN	0.286		
	MIN, MAX	0.009, 5.006		
	5%, 95%	0.094, 0.914		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	0.376, 0.277		
	SD, SE	0.3241, 0.0478		
	MEDIAN	0.279		
	MIN, MAX	0.006, 1.768		
	5%, 95%	0.107, 0.928		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	0.391, 0.285		
	SD, SE	0.4161, 0.0588		
	MEDIAN	0.312		
	MIN, MAX	0.009, 2.850		
	5%, 95%	0.116, 1.063		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438485

Final Draft: 22 October 2003

Page 516 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 122 of 264)

Biomarker: Trans-3-hydroxycotinine ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	1.771, 1.308		
	SD, SE	1.5987, 0.2261		
	MEDIAN	1.384		
	MIN, MAX	0.069, 9.247		
	5%, 95%	0.310, 4.979		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	2.342, 1.529		
	SD, SE	3.6619, 0.5231		
	MEDIAN	1.485		
	MIN, MAX	0.047, 26.046		
	5%, 95%	0.487, 4.754		
	# of BLQ/ALQ Values	0/0		
Week 3	N	46		NA
	MEAN, GEO MEAN	1.955, 1.445		
	SD, SE	1.6865, 0.2487		
	MEDIAN	1.452		
	MIN, MAX	0.033, 9.197		
	5%, 95%	0.558, 4.830		
	# of BLQ/ALQ Values	0/0		
Overall†	N	50		NA
	MEAN, GEO MEAN	2.034, 1.486		
	SD, SE	2.1649, 0.3062		
	MEDIAN	1.622		
	MIN, MAX	0.050, 14.830		
	5%, 95%	0.603, 5.530		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

† Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438486

Final Draft: 22 October 2003

Page 517 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 123 of 264)

Biomarker: Trans-3-hydroxycotinine (ng/mL)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	3549.7, 2312.1	4.4, 2.2	
	SD, SE	3173.27, 448.77	9.97, 1.24	
	MEDIAN	3110.5	1.4	
	MIN, MAX	30.1, 17333.8	1.0, 77.2	
	5%, 95%	422.2, 9882.6	1.0, 16.4	
	# of BLQ/ALQ Values	0/0	22/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	4688.4, 3050.3	6.2, 2.4	
	SD, SE	3986.05, 569.44	17.70, 2.19	
	MEDIAN	3435.7	1.7	
	MIN, MAX	26.9, 18865.3	1.0, 135.0	
	5%, 95%	692.4, 13308.1	1.0, 21.4	
	# of BLQ/ALQ Values	0/0	17/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	3636.9, 2545.4	3.6, 2.0	
	SD, SE	2820.50, 415.86	7.31, 0.91	
	MEDIAN	3045.4	1.3	
	MIN, MAX	20.4, 15599.2	1.0, 56.0	
	5%, 95%	525.1, 8394.0	1.0, 10.9	
	# of BLQ/ALQ Values	0/0	30/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	3928.4, 2775.7	4.7, 2.4	
	SD, SE	2928.37, 414.13	9.29, 1.15	
	MEDIAN	3463.0	1.8	
	MIN, MAX	25.8, 13970.9	1.0, 52.6	
	5%, 95%	601.4, 8965.5	1.0, 14.3	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438487

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 124 of 264)

Biomarker: Trans-3-hydroxycotinine (nmol/L)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	18469.2, 12030.0	23.1, 11.4	
	SD, SE	16510.52, 2334.94	51.89, 6.44	
	MEDIAN	16183.9	7.3	
	MIN, MAX	156.6, 90187.8	5.2, 401.7	
	5%, 95%	2196.7, 51419.2	5.2, 85.3	
	# of BLQ/ALQ Values	0/0	22/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	24393.8, 15870.9	32.3, 12.6	
	SD, SE	20739.45, 2962.78	92.07, 11.42	
	MEDIAN	17875.9	8.8	
	MIN, MAX	140.0, 98156.2	5.2, 702.4	
	5%, 95%	3602.6, 69242.0	5.2, 111.3	
	# of BLQ/ALQ Values	0/0	17/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	18922.7, 13243.4	18.5, 10.2	
	SD, SE	14675.07, 2163.72	38.06, 4.72	
	MEDIAN	15845.0	6.8	
	MIN, MAX	106.1, 81162.6	5.2, 291.4	
	5%, 95%	2732.1, 43674.0	5.2, 56.7	
	# of BLQ/ALQ Values	0/0	30/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	20439.3, 14441.8	24.7, 12.6	
	SD, SE	15236.32, 2154.74	48.35, 6.00	
	MEDIAN	18017.8	9.3	
	MIN, MAX	134.2, 72690.6	5.2, 273.7	
	5%, 95%	3129.3, 46647.3	5.2, 74.6	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438488

Final Draft: 22 October 2003

Page 519 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 125 of 264)

Biomarker: Trans-3-hydroxycotinine ((ng/mL)/cigarette per day)		Analytical Lab: Harrogate	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	237.0, 177.6	
	SD, SE	172.16, 24.35	
	MEDIAN	195.5	
	MIN, MAX	10.0, 648.2	
	5%, 95%	47.8, 607.6	
	# of BLQ/ALQ Values	0/0	
Week 2	N	49	
	MEAN, GEO MEAN	356.4, 246.1	
	SD, SE	330.14, 47.16	
	MEDIAN	271.8	
	MIN, MAX	9.0, 1631.9	
	5%, 95%	82.2, 942.6	
	# of BLQ/ALQ Values	0/0	
Week 3	N	46	
	MEAN, GEO MEAN	291.2, 202.9	
	SD, SE	303.79, 44.79	
	MEDIAN	197.5	
	MIN, MAX	6.8, 1850.6	
	5%, 95%	65.3, 820.7	
	# of BLQ/ALQ Values	0/0	
Overall*	N	50	
	MEAN, GEO MEAN	297.1, 220.8	
	SD, SE	239.90, 33.93	
	MEDIAN	224.3	
	MIN, MAX	8.6, 1763.3	
	5%, 95%	78.0, 801.2	
			NA

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438489

Final Draft: 22 October 2003

Page 520 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 126 of 264)

Biomarker: Trans-3-hydroxycotinine ((nmol/L)/cigarette per day)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	1232.9, 924.1		
	SD, SE	895.77, 126.68		
	MEDIAN	1017.1		
	MIN, MAX	52.2, 3372.8		
	5%, 95%	248.6, 3161.5		
Week 2	# of BLQ/ALQ Values	0/0		NA
	N	49		
	MEAN, GEO MEAN	1854.4, 1280.5		
	SD, SE	1717.72, 245.39		
	MEDIAN	1414.4		
	MIN, MAX	46.7, 8490.8		
Week 3	5%, 95%	427.4, 4904.3		NA
	# of BLQ/ALQ Values	0/0		
	N	46		
	MEAN, GEO MEAN	1515.2, 1055.7		
	SD, SE	1580.61, 233.05		
	MEDIAN	1027.4		
Overall ^b	MIN, MAX	35.4, 9628.8		NA
	5%, 95%	339.8, 4269.9		
	# of BLQ/ALQ Values	0/0		
	N	50		
	MEAN, GEO MEAN	1545.7, 1148.6		
	SD, SE	1248.24, 176.53		
	MEDIAN	1167.1		
	MIN, MAX	44.8, 6573.1		
	5%, 95%	405.8, 4168.4		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438490

Final Draft: 22 October 2003

Page 521 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 127 of 264)

Biomarker: Trans-3-hydroxycotinine-O-glucuronide (nmol/24hr)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	49	53	<.0001
	MEAN, GEO MEAN	11096.179, 6918.753	9.268, NA	
	SD, SE	10472.8752, 1496.1250	17.2617, 2.3711	
	MEDIAN	8366.015	2.106	
	MIN, MAX	197.400, 56537.828	0.000, 86.504	
	5%, 95%	757.770, 26230.442	0.000, 52.260	
	# of BLQ/ALQ Values	0/0	22/0	
Week 2	N	49	59	<.0001
	MEAN, GEO MEAN	10165.213, 7180.455	13.668, NA	
	SD, SE	7498.0883, 1071.1555	30.4127, 3.9594	
	MEDIAN	8992.596	1.575	
	MIN, MAX	126.000, 38811.750	0.000, 202.270	
	5%, 95%	622.537, 24231.808	0.000, 62.122	
	# of BLQ/ALQ Values	0/0	17/0	
Week 3	N	45	61	<.0001
	MEAN, GEO MEAN	12310.192, 8164.712	8.349, NA	
	SD, SE	11374.8476, 1695.6622	18.7129, 2.3959	
	MEDIAN	8468.655	1.050	
	MIN, MAX	160.858, 64170.700	0.000, 88.660	
	5%, 95%	1725.522, 31402.440	0.000, 42.273	
	# of BLQ/ALQ Values	0/0	30/0	
Overall ^b	N	50	64	<.0001
	MEAN, GEO MEAN	10913.713, 7675.781	10.045, NA	
	SD, SE	8872.2538, 1254.7262	19.3895, 2.4237	
	MEDIAN	9018.318	2.457	
	MIN, MAX	161.423, 49042.882	0.000, 104.787	
	5%, 95%	828.268, 27010.976	0.000, 49.847	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438491

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 128 of 264)

Biomarker: Trans-3-hydroxycotinine-O-glucuronide ((nmol/24hr)/cigarette per day)		Analytical Lab: Harrogate		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	49		NA
	MEAN, GEO MEAN	695.999, 530.594		
	SD, SE	448.5707, 64.0815		
	MEDIAN	671.090		
	MIN, MAX	43.617, 1884.594		
	5%, 95%	65.800, 1670.809		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	793.931, 579.332		
	SD, SE	811.6069, 115.9438		
	MEDIAN	626.919		
	MIN, MAX	34.585, 5423.915		
	5%, 95%	175.088, 1661.556		
	# of BLQ/ALQ Values	0/0		
Week 3	N	45		NA
	MEAN, GEO MEAN	828.559, 637.667		
	SD, SE	590.4088, 88.0129		
	MEDIAN	673.095		
	MIN, MAX	35.637, 3329.928		
	5%, 95%	236.928, 1723.842		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	769.302, 619.089		
	SD, SE	518.4089, 73.3141		
	MEDIAN	707.376		
	MIN, MAX	37.946, 3355.093		
	5%, 95%	230.597, 1545.608		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., ≤ 1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438492

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 129 of 264)

Biomarker: Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	49	53	<.0001
	MEAN, GEO MEAN	8.953, 5.755	0.006, NA	
	SD, SE	7.6799, 1.0971	0.0114, 0.0016	
	MEDIAN	6.754	0.002	
	MIN, MAX	0.182, 37.904	0.000, 0.053	
	5%, 95%	0.365, 24.215	0.000, 0.034	
	# of BLQ/ALQ Values	0/0	22/0	
Week 2	N	49	59	<.0001
	MEAN, GEO MEAN	8.344, 5.542	0.009, NA	
	SD, SE	7.7423, 1.1060	0.0188, 0.0024	
	MEDIAN	5.726	0.001	
	MIN, MAX	0.141, 37.773	0.000, 0.105	
	5%, 95%	0.539, 24.592	0.000, 0.053	
	# of BLQ/ALQ Values	0/0	17/0	
Week 3	N	45	61	<.0001
	MEAN, GEO MEAN	10.066, 6.491	0.005, NA	
	SD, SE	9.7261, 1.4499	0.0101, 0.0013	
	MEDIAN	6.677	0.001	
	MIN, MAX	0.141, 41.198	0.000, 0.050	
	5%, 95%	1.718, 30.778	0.000, 0.030	
	# of BLQ/ALQ Values	0/0	30/0	
Overall ^b	N	50	64	<.0001
	MEAN, GEO MEAN	9.000, 6.118	0.006, NA	
	SD, SE	7.9341, 1.1220	0.0116, 0.0014	
	MEDIAN	6.640	0.002	
	MIN, MAX	0.156, 38.958	0.000, 0.052	
	5%, 95%	0.813, 26.074	0.000, 0.036	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234" will be used as "1.234") for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438493

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 130 of 264)

Biomarker: Trans-3-hydroxycotinine-O-glucuronide ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	49		NA
	MEAN, GEO MEAN	0.618, 0.441		
	SD, SE	0.6338, 0.0905		
	MEDIAN	0.507		
	MIN, MAX	0.020, 3.948		
	5%, 95%	0.091, 1.523		
	# of BLQ/ALQ Values	0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	0.755, 0.447		
	SD, SE	1.5032, 0.2147		
	MEDIAN	0.437		
	MIN, MAX	0.018, 10.734		
	5%, 95%	0.135, 1.381		
	# of BLQ/ALQ Values	0/0		
Week 3	N	45		NA
	MEAN, GEO MEAN	0.722, 0.507		
	SD, SE	0.8347, 0.1244		
	MEDIAN	0.560		
	MIN, MAX	0.020, 3.679		
	5%, 95%	0.217, 1.231		
	# of BLQ/ALQ Values	0/0		
Overall*	N	50		NA
	MEAN, GEO MEAN	0.700, 0.494		
	SD, SE	0.9391, 0.1328		
	MEDIAN	0.514		
	MIN, MAX	0.019, 6.787		
	5%, 95%	0.177, 1.316		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438494

Final Draft: 22 October 2003

Page 525 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 131 of 264)

Biomarker: Trans-3-hydroxycotinine-O-glucuronide (nmol/L) Analytical Lab: Harrogate				
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	49	53	<.0001
	MEAN, GEO MEAN	6895.8, 4024.9	6.0, NA	
	SD, SE	7654.61, 1093.52	14.26, 1.96	
	MEDIAN	5136.9	2.1	
	MIN, MAX	79.6, 48117.3	0.0, 98.3	
	5%, 95%	649.9, 16292.2	0.0, 21.9	
	# of BLQ/ALQ Values	0/0	22/0	
Week 2	N	49	59	<.0001
	MEAN, GEO MEAN	6711.8, 4641.4	8.8, NA	
	SD, SE	5108.69, 729.81	25.07, 3.26	
	MEDIAN	5545.9	1.6	
	MIN, MAX	140.0, 23215.8	0.0, 179.0	
	5%, 95%	596.3, 15749.0	0.0, 38.0	
	# of BLQ/ALQ Values	0/0	17/0	
Week 3	N	45	61	<.0001
	MEAN, GEO MEAN	7528.7, 4762.9	4.5, NA	
	SD, SE	8062.18, 1201.84	10.35, 1.33	
	MEDIAN	5225.9	0.5	
	MIN, MAX	153.5, 40612.0	0.0, 68.2	
	5%, 95%	927.7, 29168.5	0.0, 24.5	
	# of BLQ/ALQ Values	0/0	30/0	
Overall ^b	N	50	64	<.0001
	MEAN, GEO MEAN	6902.1, 4770.7	6.4, NA	
	SD, SE	5566.90, 787.28	14.10, 1.76	
	MEDIAN	5704.9	1.7	
	MIN, MAX	144.5, 25999.9	0.0, 83.3	
	5%, 95%	640.7, 19989.6	0.0, 22.2	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438495

Final Draft: 22 October 2003

Page 526 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 132 of 264)

Biomarker: Trans-3-hydroxycotinine-O-glucuronide ((nmol/L)/cigarette per day)		Analytical Lab: Harrogate		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	49		NA
	MEAN, GEO MEAN	433.3, 308.7		
	SD, SE	348.28, 49.75		
	MEDIAN	366.9		
	MIN, MAX	39.8, 1603.9		
	5%, 95%	58.1, 1099.4		
# of BLQ/ALQ Values		0/0		
Week 2	N	49		NA
	MEAN, GEO MEAN	538.1, 374.5		
	SD, SE	578.57, 82.65		
	MEDIAN	388.1		
	MIN, MAX	33.1, 3499.3		
	5%, 95%	76.7, 1620.3		
# of BLQ/ALQ Values		0/0		
Week 3	N	45		NA
	MEAN, GEO MEAN	595.7, 372.0		
	SD, SE	899.83, 134.14		
	MEDIAN	367.3		
	MIN, MAX	15.5, 5946.3		
	5%, 95%	125.4, 1673.6		
# of BLQ/ALQ Values		0/0		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	520.2, 382.8		
	SD, SE	502.97, 71.13		
	MEDIAN	397.4		
	MIN, MAX	35.6, 3376.2		
	5%, 95%	133.6, 1077.6		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438496

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 133 of 264)

Biomarker: Cotinine (nmol/24hr)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	7	0.0034
	MEAN, GEO MEAN	8116.241, 7377.365	9819, 7.923	
	SD, SE	3337.3914, 1362.4844	8.2449, 3.1163	
	MEDIAN	9239.023	7.062	
	MIN, MAX	3100.528, 11659.550	3.720, 27.797	
	5%, 95%	3100.528, 11659.550	3.720, 27.797	
	# of BLQ/ALQ Values	0/0	6/0	
Week 2	N	6	8	0.0024
	MEAN, GEO MEAN	8657.223, 8169.359	7.179, 6.747	
	SD, SE	3203.9834, 1308.0207	2.4766, 0.8756	
	MEDIAN	8162.925	7.673	
	MIN, MAX	4574.775, 13936.670	3.224, 10.540	
	5%, 95%	4574.775, 13936.670	3.224, 10.540	
	# of BLQ/ALQ Values	0/0	8/0	
Week 3	N	5	7	0.0058
	MEAN, GEO MEAN	7331.938, 6175.173	6.454, 6.143	
	SD, SE	4110.3879, 1838.2214	2.2246, 0.8408	
	MEDIAN	7564.865	5.828	
	MIN, MAX	2098.704, 12059.465	3.906, 9.920	
	5%, 95%	2098.704, 12059.465	3.906, 9.920	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	6	8	0.0024
	MEAN, GEO MEAN	8075.004, 7437.279	7.852, 7.377	
	SD, SE	3105.3617, 1267.7586	2.8719, 1.0154	
	MEDIAN	9221.998	7.854	
	MIN, MAX	3258.002, 10736.417	3.617, 13.134	
	5%, 95%	3258.002, 10736.417	3.617, 13.134	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438497

Final Draft: 22 October 2003

Page 528 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 134 of 264)

Biomarker: Cotinine (µg/24hr)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	7	0.0034
	MEAN, GEO MEAN	1430.082, 1299.892	1.730, 1.396	
	SD, SE	588.0485, 240.0698	1.4529, 0.5492	
	MEDIAN	1627.916	1.244	
	MIN, MAX	546.313, 2054.413	0.655, 4.898	
	5%, 95%	546.313, 2054.413	0.655, 4.898	
	# of BLQ/ALQ Values	0/0	6/0	
Week 2	N	6	8	0.0024
	MEAN, GEO MEAN	1525.403, 1439.441	1.265, 1.189	
	SD, SE	564.5419, 230.4733	0.4362, 0.1542	
	MEDIAN	1438.308	1.352	
	MIN, MAX	806.075, 2455.641	0.568, 1.857	
	5%, 95%	806.075, 2455.641	0.568, 1.857	
	# of BLQ/ALQ Values	0/0	8/0	
Week 3	N	5	7	0.0058
	MEAN, GEO MEAN	1291.888, 1088.066	1.137, 1.082	
	SD, SE	724.2504, 323.8946	0.3920, 0.1482	
	MEDIAN	1332.929	1.027	
	MIN, MAX	369.792, 2124.878	0.688, 1.748	
	5%, 95%	369.792, 2124.878	0.688, 1.748	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	6	8	0.0024
	MEAN, GEO MEAN	1422.816, 1310.449	1.383, 1.300	
	SD, SE	547.1647, 223.3791	0.5060, 0.1789	
	MEDIAN	1624.916	1.384	
	MIN, MAX	574.060, 1891.757	0.637, 2.314	
	5%, 95%	574.060, 1891.757	0.637, 2.314	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438498

Final Draft: 22 October 2003

Page 529 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 135 of 264)

Biomarker: Cotinine ((nmol/24hr)/cigarette per day)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	480.942, 449.009		
	SD, SE	209.8036, 85.6520		
	MEDIAN	433.268		
	MIN, MAX	278.469, 870.573		
	5%, 95%	278.469, 870.573		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	728.933, 619.083		
	SD, SE	504.0549, 205.7796		
	MEDIAN	577.156		
	MIN, MAX	350.203, 1683.665		
	5%, 95%	350.203, 1683.665		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	744.731, 565.317		
	SD, SE	631.7633, 282.5332		
	MEDIAN	378.243		
	MIN, MAX	249.386, 1741.285		
	5%, 95%	249.386, 1741.285		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	6		NA
	MEAN, GEO MEAN	630.928, 552.357		
	SD, SE	372.9587, 152.2598		
	MEDIAN	480.530		
	MIN, MAX	292.686, 1259.423		
	5%, 95%	292.686, 1259.423		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438499

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 136 of 264)

Biomarker: Cotinine ((µg/24hr)/cigarette per day) Analytical Lab: INBIFO			
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	6	
	MEAN, GEO MEAN	84.742, 79.115	
	SD, SE	36.9674, 15.0919	
	MEDIAN	76.342	
	MIN, MAX	49.066, 153.395	
	5%, 95%	49.066, 153.395	
	# of BLQ/ALQ Values	0/0	
Week 2	N	6	
	MEAN, GEO MEAN	128.438, 109.083	
	SD, SE	88.8144, 36.2583	
	MEDIAN	101.695	
	MIN, MAX	61.706, 296.662	
	5%, 95%	61.706, 296.662	
	# of BLQ/ALQ Values	0/0	
Week 3	N	5	
	MEAN, GEO MEAN	131.222, 99.609	
	SD, SE	111.3169, 49.7824	
	MEDIAN	66.646	
	MIN, MAX	43.942, 306.815	
	5%, 95%	43.942, 306.815	
	# of BLQ/ALQ Values	0/0	
Overall*	N	6	
	MEAN, GEO MEAN	111.170, 97.325	
	SD, SE	65.7157, 26.8283	
	MEDIAN	84.669	
	MIN, MAX	51.571, 221.911	
	5%, 95%	51.571, 221.911	
			NA

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438500

Final Draft: 22 October 2003

Page 531 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 137 of 264)

Biomarker: Cotinine (nmol/mg Creatinine)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	7	0.0032
	MEAN, GEO MEAN	6.206, 5.345	0.006, 0.006	
	SD, SE	3.4820, 1.4215	0.0034, 0.0013	
	MEDIAN	6.151	0.005	
	MIN, MAX	2.553, 11.433	0.003, 0.012	
	5%, 95%	2.553, 11.433	0.003, 0.012	
	# of BLQ/ALQ Values	0/0	6/0	
Week 2	N	6	8	0.0024
	MEAN, GEO MEAN	7.082, 6.437	0.005, 0.005	
	SD, SE	3.7617, 1.5357	0.0028, 0.0010	
	MEDIAN	5.586	0.005	
	MIN, MAX	4.231, 14.182	0.002, 0.011	
	5%, 95%	4.231, 14.182	0.002, 0.011	
	# of BLQ/ALQ Values	0/0	8/0	
Week 3	N	5	7	0.0049
	MEAN, GEO MEAN	6.752, 6.033	0.005, 0.005	
	SD, SE	3.2634, 1.4594	0.0014, 0.0005	
	MEDIAN	7.282	0.006	
	MIN, MAX	3.016, 9.978	0.003, 0.007	
	5%, 95%	3.016, 9.978	0.003, 0.007	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	6	8	0.0024
	MEAN, GEO MEAN	6.575, 5.962	0.006, 0.006	
	SD, SE	3.0766, 1.2560	0.0018, 0.0006	
	MEDIAN	6.547	0.005	
	MIN, MAX	3.296, 10.966	0.004, 0.009	
	5%, 95%	3.296, 10.966	0.004, 0.009	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438501

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 138 of 264)

Biomarker: Cotinine ($\mu\text{g}/\text{mg}$ Creatinine)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6	7	0.0026
	MEAN, GEO MEAN	1.093, 0.942	0.001, 0.001	
	SD, SE	0.6133, 0.2504	0.0005, 0.0002	
	MEDIAN	1.084	0.001	
	MIN, MAX	0.450, 2.014	0.001, 0.002	
	5%, 95%	0.450, 2.014	0.001, 0.002	
	# of BLQ/ALQ Values	0/0	6/0	
Week 2	N	6	8	0.0016
	MEAN, GEO MEAN	1.248, 1.134	0.001, NA	
	SD, SE	0.6628, 0.2706	0.0005, 0.0002	
	MEDIAN	0.984	0.001	
	MIN, MAX	0.746, 2.499	0.000, 0.002	
	5%, 95%	0.746, 2.499	0.000, 0.002	
	# of BLQ/ALQ Values	0/0	8/0	
Week 3	N	5	7	0.0021
	MEAN, GEO MEAN	1.190, 1.063	0.001, 0.001	
	SD, SE	0.5751, 0.2572	0.0000, 0.0000	
	MEDIAN	1.283	0.001	
	MIN, MAX	0.531, 1.758	0.001, 0.001	
	5%, 95%	0.531, 1.758	0.001, 0.001	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	6	8	0.0016
	MEAN, GEO MEAN	1.159, 1.051	0.001, 0.001	
	SD, SE	0.5419, 0.2212	0.0004, 0.0001	
	MEDIAN	1.154	0.001	
	MIN, MAX	0.581, 1.932	0.001, 0.002	
	5%, 95%	0.581, 1.932	0.001, 0.002	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438502

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 139 of 264)

Biomarker: Cotinine ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: INBIFO	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	6	NA
	MEAN, GEO MEAN	0.371, 0.326	
	SD, SE	0.1949, 0.0796	
	MEDIAN	0.339	
	MIN, MAX	0.147, 0.612	
	5%, 95%	0.147, 0.612	
	# of BLQ/ALQ Values	0/0	
Week 2	N	6	NA
	MEAN, GEO MEAN	0.574, 0.488	
	SD, SE	0.3286, 0.1342	
	MEDIAN	0.594	
	MIN, MAX	0.212, 1.066	
	5%, 95%	0.212, 1.066	
	# of BLQ/ALQ Values	0/0	
Week 3	N	5	NA
	MEAN, GEO MEAN	0.726, 0.553	
	SD, SE	0.5784, 0.2387	
	MEDIAN	0.624	
	MIN, MAX	0.168, 1.663	
	5%, 95%	0.168, 1.663	
	# of BLQ/ALQ Values	0/0	
Overall*	N	6	NA
	MEAN, GEO MEAN	0.529, 0.447	
	SD, SE	0.3063, 0.1250	
	MEDIAN	0.529	
	MIN, MAX	0.176, 0.994	
	5%, 95%	0.176, 0.994	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438503

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 140 of 264)

Biomarker: Cotinine ((µg/mg Creatinine)/cigarette per day)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6		NA
	MEAN, GEO MEAN	0.065, 0.057		
	SD, SE	0.0345, 0.0141		
	MEDIAN	0.060		
	MIN, MAX	0.026, 0.108		
	5%, 95%	0.026, 0.108		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	0.101, 0.086		
	SD, SE	0.0581, 0.0237		
	MEDIAN	0.105		
	MIN, MAX	0.037, 0.188		
	5%, 95%	0.037, 0.188		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	0.128, 0.098		
	SD, SE	0.1018, 0.0455		
	MEDIAN	0.110		
	MIN, MAX	0.030, 0.293		
	5%, 95%	0.030, 0.293		
	# of BLQ/ALQ Values	0/0		
Overall*	N	6		NA
	MEAN, GEO MEAN	0.093, 0.079		
	SD, SE	0.0540, 0.0220		
	MEDIAN	0.094		
	MIN, MAX	0.031, 0.175		
	5%, 95%	0.031, 0.175		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438504

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 141 of 264)

Biomarker: Cotinine (nmol/L)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	7	0.0021
	MEAN, GEO MEAN	5138.7, 4383.0	5.6, 4.1	
	SD, SE	3563.54, 1454.81	6.73, 2.54	
	MEDIAN	4048.8	3.1	
	MIN, MAX	2279.8, 12007.9	3.1, 20.9	
	5%, 95%	2279.8, 12007.9	3.1, 20.9	
	# of BLQ/ALQ Values	0/0	6/0	
Week 2	N	6	8	0.0008
	MEAN, GEO MEAN	5341.9, 4848.5	3.1, 3.1	
	SD, SE	2622.04, 1070.44	0.00, 0.00	
	MEDIAN	4597.2	3.1	
	MIN, MAX	2527.5, 9702.2	3.1, 3.1	
	5%, 95%	2527.5, 9702.2	3.1, 3.1	
	# of BLQ/ALQ Values	0/0	8/0	
Week 3	N	5	7	0.0021
	MEAN, GEO MEAN	4021.5, 3476.2	3.1, 3.1	
	SD, SE	2413.87, 1079.52	0.00, 0.00	
	MEDIAN	3087.7	3.1	
	MIN, MAX	1520.8, 7780.3	3.1, 3.1	
	5%, 95%	1520.8, 7780.3	3.1, 3.1	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	6	8	0.0012
	MEAN, GEO MEAN	4959.3, 4381.0	3.8, 3.5	
	SD, SE	2782.63, 1136.00	2.09, 0.74	
	MEDIAN	4206.5	3.1	
	MIN, MAX	2109.4, 9830.1	3.1, 9.0	
	5%, 95%	2109.4, 9830.1	3.1, 9.0	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438505

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 142 of 264)

Biomarker: Cotinine (ng/mL)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6	7	0.0021
	MEAN, GEO MEAN	905.4, 772.3	1.0, 0.7	
	SD, SE	627.91, 256.34	1.21, 0.46	
	MEDIAN	713.4	0.5	
	MIN, MAX	401.7, 2115.8	0.5, 3.7	
	5%, 95%	401.7, 2115.8	0.5, 3.7	
	# of BLQ/ALQ Values	0/0	6/0	
Week 2	N	6	8	0.0008
	MEAN, GEO MEAN	941.2, 854.3	0.5, 0.5	
	SD, SE	462.01, 188.61	0.00, 0.00	
	MEDIAN	810.0	0.5	
	MIN, MAX	445.3, 1709.5	0.5, 0.5	
	5%, 95%	445.3, 1709.5	0.5, 0.5	
	# of BLQ/ALQ Values	0/0	8/0	
Week 3	N	5	7	0.0021
	MEAN, GEO MEAN	708.6, 612.5	0.5, 0.5	
	SD, SE	425.31, 190.20	0.00, 0.00	
	MEDIAN	544.1	0.5	
	MIN, MAX	268.0, 1370.9	0.5, 0.5	
	5%, 95%	268.0, 1370.9	0.5, 0.5	
	# of BLQ/ALQ Values	0/0	7/0	
Overall*	N	6	8	0.0012
	MEAN, GEO MEAN	873.9, 771.9	0.6, 0.6	
	SD, SE	490.31, 200.17	0.39, 0.14	
	MEDIAN	741.2	0.5	
	MIN, MAX	371.7, 1732.1	0.5, 1.6	
	5%, 95%	371.7, 1732.1	0.5, 1.6	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438506

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 143 of 264)

Biomarker: Cotinine ((nmol/L)/cigarette per day) Analytical Lab: INBIFO			
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	6	
	MEAN, GEO MEAN	349.2, 266.8	
	SD, SE	330.69, 135.00	
	MEDIAN	202.2	
	MIN, MAX	144.2, 1000.7	
	5%, 95%	144.2, 1000.7	
	# of BLQ/ALQ Values	0/0	
Week 2	N	6	
	MEAN, GEO MEAN	445.7, 367.5	
	SD, SE	306.85, 125.27	
	MEDIAN	303.7	
	MIN, MAX	176.9, 882.0	
	5%, 95%	176.9, 882.0	
	# of BLQ/ALQ Values	0/0	
Week 3	N	5	
	MEAN, GEO MEAN	405.0, 318.2	
	SD, SE	303.96, 135.93	
	MEDIAN	253.5	
	MIN, MAX	154.4, 809.9	
	5%, 95%	154.4, 809.9	
	# of BLQ/ALQ Values	0/0	
Overall*	N	6	
	MEAN, GEO MEAN	393.9, 330.4	
	SD, SE	265.41, 108.35	
	MEDIAN	295.7	
	MIN, MAX	167.2, 843.7	
	5%, 95%	167.2, 843.7	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438507

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 144 of 264)

Biomarker: Cotinine ((ng/mL)/cigarette per day)		Analytical Lab: INBIFO	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	6	
	MEAN, GEO MEAN	61.5, 47.0	
	SD, SE	58.26, 23.78	
	MEDIAN	35.7	
	MIN, MAX	25.4, 176.3	
	5%, 95%	25.4, 176.3	
	# of BLQ/ALQ Values	0/0	
Week 2	N	6	
	MEAN, GEO MEAN	78.5, 64.7	
	SD, SE	54.07, 22.07	
	MEDIAN	53.5	
	MIN, MAX	31.2, 155.4	
	5%, 95%	31.2, 155.4	
	# of BLQ/ALQ Values	0/0	
Week 3	N	5	
	MEAN, GEO MEAN	71.4, 56.1	
	SD, SE	53.54, 23.94	
	MEDIAN	44.7	
	MIN, MAX	27.2, 142.7	
	5%, 95%	27.2, 142.7	
	# of BLQ/ALQ Values	0/0	
Overall*	N	6	
	MEAN, GEO MEAN	69.4, 58.2	
	SD, SE	46.72, 19.07	
	MEDIAN	52.2	
	MIN, MAX	29.5, 148.6	
	5%, 95%	29.5, 148.6	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438508

Final Draft: 22 October 2003

Page 539 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 145 of 264)

Biomarker: Cotinine-N-glucuronide (nmol/24hr) Analytical Lab: INBIFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	5	0.0081
	MEAN, GEO MEAN	13422.559, 9233.175	17.266, 16.074	
	SD, SE	8208.4761, 3351.0963	7.0648, 3.1595	
	MEDIAN	12610.540	16.116	
	MIN, MAX	797.096, 24184.869	9.480, 25.343	
	5%, 95%	797.096, 24184.869	9.480, 25.343	
	# of BLQ/ALQ Values	0/0	5/0	
Week 2	N	6	7	0.0034
	MEAN, GEO MEAN	13285.550, 10994.917	18.424, 17.167	
	SD, SE	6499.2379, 2653.3027	6.8053, 2.5722	
	MEDIAN	14471.774	21.725	
	MIN, MAX	2320.420, 19683.264	8.216, 26.860	
	5%, 95%	2320.420, 19683.264	8.216, 26.860	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	5	6	0.0081
	MEAN, GEO MEAN	11027.932, 6237.609	14.976, 14.454	
	SD, SE	7390.1613, 3304.9806	4.5130, 1.8424	
	MEDIAN	12845.595	14.536	
	MIN, MAX	339.066, 19365.855	9.954, 22.910	
	5%, 95%	339.066, 19365.855	9.954, 22.910	
	# of BLQ/ALQ Values	0/0	6/0	
Overall ^b	N	6	8	0.0024
	MEAN, GEO MEAN	12803.241, 9518.732	17.115, 16.315	
	SD, SE	7083.9876, 2892.0258	5.3727, 1.8995	
	MEDIAN	13680.040	16.980	
	MIN, MAX	1152.194, 21077.996	9.217, 24.028	
	5%, 95%	1152.194, 21077.996	9.217, 24.028	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438509

Final Draft: 22 October 2003

Page 540 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 146 of 264)

Biomarker: Cotinine-N-glucuronide (nmol/24hr)/cigarette per day		Analytical Lab: INBIPO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	748.939, 561.959		
	SD, SE	646.9264, 264.1066		
	MEDIAN	588.578		
	MIN, MAX	132.849, 2015.406		
	5%, 95%	132.849, 2015.406		
Week 2	# of BLQ/ALQ Values	0/0		NA
	N	6		
	MEAN, GEO MEAN	1185.202, 833.207		
	SD, SE	1099.5289, 448.8808		
	MEDIAN	723.589		
	MIN, MAX	232.042, 3148.998		
Week 3	5%, 95%	232.042, 3148.998		NA
	# of BLQ/ALQ Values	0/0		
	N	5		
	MEAN, GEO MEAN	1052.329, 571.033		
	SD, SE	1013.2672, 453.1469		
	MEDIAN	642.280		
Overall ^b	MIN, MAX	56.511, 2541.121		NA
	5%, 95%	56.511, 2541.121		
	# of BLQ/ALQ Values	0/0		
	N	6		
	MEAN, GEO MEAN	976.310, 695.682		
	SD, SE	786.1268, 320.9349		
	MEDIAN	660.795		
	MIN, MAX	140.467, 2099.895		
	5%, 95%	140.467, 2099.895		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438510

Final Draft: 22 October 2003

Page 541 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 147 of 264)

Biomarker: Cotinine-N-glucuronide (nmol/mg Creatinine)		Analytical Lab: INB/FO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6	5	0.0080
	MEAN, GEO MEAN	9.727, 6.689	0.013, 0.012	
	SD, SE	6.1408, 2.5070	0.0070, 0.0031	
	MEDIAN	10.503	0.012	
	MIN, MAX	0.656, 16.992	0.007, 0.025	
	5%, 95%	0.656, 16.992	0.007, 0.025	
	# of BLQ/ALQ Values	0/0	5/0	
Week 2	N	6	7	0.0034
	MEAN, GEO MEAN	10.292, 8.664	0.013, 0.011	
	SD, SE	5.4364, 2.2194	0.0079, 0.0030	
	MEDIAN	11.178	0.010	
	MIN, MAX	2.423, 17.741	0.005, 0.028	
	5%, 95%	2.423, 17.741	0.005, 0.028	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	5	6	0.0078
	MEAN, GEO MEAN	9.621, 6.094	0.013, 0.013	
	SD, SE	6.5461, 2.9275	0.0037, 0.0015	
	MEDIAN	12.366	0.015	
	MIN, MAX	0.605, 15.637	0.008, 0.016	
	5%, 95%	0.605, 15.637	0.008, 0.016	
	# of BLQ/ALQ Values	0/0	6/0	
Overall*	N	6	8	0.0024
	MEAN, GEO MEAN	9.857, 7.519	0.014, 0.013	
	SD, SE	5.7580, 2.3307	0.0055, 0.0019	
	MEDIAN	11.042	0.013	
	MIN, MAX	1.228, 16.790	0.007, 0.022	
	5%, 95%	1.228, 16.790	0.007, 0.022	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438511

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2 1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 148 of 264)

Biomarker: Cotinine-N-glucuronide ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: INBIFO	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	6	
	MEAN, GEO MEAN	0.543, 0.407	
	SD, SE	0.4628, 0.1889	
	MEDIAN	0.392	
	MIN, MAX	0.109, 1.416	
	5%, 95%	0.109, 1.416	
	# of BLQ/ALQ Values	0/0	
Week 2	N	6	
	MEAN, GEO MEAN	0.888, 0.656	
	SD, SE	0.7346, 0.2999	
	MEDIAN	0.592	
	MIN, MAX	0.242, 1.993	
	5%, 95%	0.242, 1.993	
	# of BLQ/ALQ Values	0/0	
Week 3	N	5	
	MEAN, GEO MEAN	0.945, 0.558	
	SD, SE	0.9479, 0.4239	
	MEDIAN	0.618	
	MIN, MAX	0.101, 2.427	
	5%, 95%	0.101, 2.427	
	# of BLQ/ALQ Values	0/0	
Overall*	N	6	
	MEAN, GEO MEAN	0.764, 0.553	
	SD, SE	0.6189, 0.2527	
	MEDIAN	0.539	
	MIN, MAX	0.151, 1.618	
	5%, 95%	0.151, 1.618	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438512

Final Draft: 22 October 2003

Page 543 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 149 of 264)

Biomarker: Cotinine-N-glucuronide (nmol/L)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	5	0.0055
	MEAN, GEO MEAN	9217.7, 5485.6	7.9, 7.9	
	SD, SE	9594.01, 3916.74	0.00, 0.00	
	MEDIAN	7145.9	7.9	
	MIN, MAX	586.1, 27798.7	7.9, 7.9	
	5%, 95%	586.1, 27798.7	7.9, 7.9	
	# of BLQ/ALQ Values	0/0	5/0	
Week 2	N	6	7	0.0015
	MEAN, GEO MEAN	9311.5, 6525.5	7.9, 7.9	
	SD, SE	7584.50, 3096.36	0.00, 0.00	
	MEDIAN	6886.9	7.9	
	MIN, MAX	1282.0, 21164.8	7.9, 7.9	
	5%, 95%	1282.0, 21164.8	7.9, 7.9	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	5	6	0.0039
	MEAN, GEO MEAN	5950.2, 3511.4	7.9, 7.9	
	SD, SE	4438.14, 1984.80	0.00, 0.00	
	MEDIAN	5243.1	7.9	
	MIN, MAX	245.7, 12494.1	7.9, 7.9	
	5%, 95%	245.7, 12494.1	7.9, 7.9	
	# of BLQ/ALQ Values	0/0	6/0	
Overall ^b	N	6	8	0.0008
	MEAN, GEO MEAN	8503.8, 5651.7	7.9, 7.9	
	SD, SE	7002.82, 2858.89	0.00, 0.00	
	MEDIAN	6639.0	7.9	
	MIN, MAX	704.6, 20485.9	7.9, 7.9	
	5%, 95%	704.6, 20485.9	7.9, 7.9	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438513

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 150 of 264)

Biomarker: Cotinine-N-glucuronide ((nmol/L)/cigarette per day)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	595.8, 333.9		
	SD, SE	849.24, 346.70		
	MEDIAN	293.4		
	MIN, MAX	97.7, 2316.6		
	5%, 95%	97.7, 2316.6		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	791.5, 494.5		
	SD, SE	749.41, 305.95		
	MEDIAN	510.7		
	MIN, MAX	128.2, 1924.1		
	5%, 95%	128.2, 1924.1		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	557.2, 321.5		
	SD, SE	516.34, 230.92		
	MEDIAN	262.2		
	MIN, MAX	41.0, 1181.9		
	5%, 95%	41.0, 1181.9		
	# of BLQ/ALQ Values	0/0		
Overall*	N	6		NA
	MEAN, GEO MEAN	649.3, 419.5		
	SD, SE	628.04, 256.40		
	MEDIAN	430.3		
	MIN, MAX	89.0, 1760.6		
	5%, 95%	89.0, 1760.6		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438514

Final Draft: 22 October 2003

Page 545 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 151 of 264)

Biomarker: NNAL (pg/24hr)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	4	7	0.0107
	MEAN, GEO MEAN	149728.625, 135488.373	17892.457, 15800.916	
	SD, SE	67405.5472, 33702.7736	9736.3366, 3679.9893	
	MEDIAN	159918.500	12688.000	
	MIN, MAX	62452.500, 216625.000	8112.000, 33363.200	
	5%, 95%	62452.500, 216625.000	8112.000, 33363.200	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	4	7	0.0106
	MEAN, GEO MEAN	197474.000, 185687.328	20190.857, 18701.256	
	SD, SE	75490.3263, 37745.1631	7792.0061, 2945.1015	
	MEDIAN	197263.000	21320.000	
	MIN, MAX	105754.000, 289616.000	7800.000, 33280.000	
	5%, 95%	105754.000, 289616.000	7800.000, 33280.000	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	4	7	0.0107
	MEAN, GEO MEAN	173601.313, 161533.445	19041.657, 17423.551	
	SD, SE	67681.6128, 33840.8064	8398.6587, 3174.3946	
	MEDIAN	186319.000	17160.000	
	MIN, MAX	84103.250, 237664.000	7956.000, 33321.600	
	5%, 95%	84103.250, 237664.000	7956.000, 33321.600	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438515

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 152 of 264)

Biomarker: NNAL (pmol/24hr)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	4	7	0.0107
	MEAN, GEO MEAN	715.703, 647.635	85.526, 75.528	
	SD, SE	322.1986, 161.0993	46.5396, 17.5903	
	MEDIAN	764.411	60.649	
	MIN, MAX	298.523, 1035.468	38.775, 159.476	
	5%, 95%	298.523, 1035.468	38.775, 159.476	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	4	7	0.0106
	MEAN, GEO MEAN	943.926, 887.585	96.512, 89.392	
	SD, SE	360.8436, 180.4218	37.2457, 14.0776	
	MEDIAN	942.918	101.910	
	MIN, MAX	505.504, 1384.364	37.284, 159.078	
	5%, 95%	505.504, 1384.364	37.284, 159.078	
	# of BLQ/ALQ Values	0/0	7/0	
Overall*	N	4	7	0.0107
	MEAN, GEO MEAN	829.815, 772.130	91.019, 83.285	
	SD, SE	323.5181, 161.7590	40.1454, 15.1735	
	MEDIAN	890.606	82.025	
	MIN, MAX	402.014, 1136.034	38.030, 159.277	
	5%, 95%	402.014, 1136.034	38.030, 159.277	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438516

Final Draft: 22 October 2003

Page 547 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 153 of 264)

Biomarker: NNAL ((pg/24hr)/cigarette per day)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	4		NA
	MEAN, GEO MEAN	10190.435, 8614.184		
	SD, SE	6353.7672, 3176.8836		
	MEDIAN	9360.478		
	MIN, MAX	3469.583, 18571.200		
	5%, 95%	3469.583, 18571.200		
	# of BLQ/ALQ Values	0/0		
Week 3	N	4		NA
	MEAN, GEO MEAN	12847.485, 11279.740		
	SD, SE	7864.4053, 3932.2027		
	MEDIAN	10690.025		
	MIN, MAX	5875.222, 24134.667		
	5%, 95%	5875.222, 24134.667		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	4		NA
	MEAN, GEO MEAN	11518.960, 9998.806		
	SD, SE	7040.1168, 3520.0584		
	MEDIAN	10025.252		
	MIN, MAX	4672.403, 21352.934		
	5%, 95%	4672.403, 21352.934		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438517

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 154 of 264)

Biomarker: NNAL ((pmol/24hr)/cigarette per day) Analytical Lab: INBIFO

Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	4		NA
	MEAN, GEO MEAN	48.710, 41.176		
	SD, SE	30.3707, 15.1853		
	MEDIAN	44.743		
	MIN, MAX	16.585, 88.770		
	5%, 95%	16.585, 88.770		
	# of BLQ/ALQ Values	0/0		
Week 3	N	4		NA
	MEAN, GEO MEAN	61.411, 53.917		
	SD, SE	37.5918, 18.7959		
	MEDIAN	51.099		
	MIN, MAX	28.084, 115.364		
	5%, 95%	28.084, 115.364		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	4		NA
	MEAN, GEO MEAN	55.061, 47.795		
	SD, SE	33.6514, 16.8257		
	MEDIAN	47.921		
	MIN, MAX	22.335, 102.067		
	5%, 95%	22.335, 102.067		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 155 of 264)

Biomarker: NNAL (pg/mg Creatinine)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	4	7	0.0182
	MEAN, GEO MEAN	130.848, 94.734	14.314, 10.611	
	SD, SE	114.7662, 57.3831	11.6080, 4.3874	
	MEDIAN	101.297	7.542	
	MIN, MAX	29.054, 291.743	3.645, 32.298	
	5%, 95%	29.054, 291.743	3.645, 32.298	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	4	7	0.0107
	MEAN, GEO MEAN	133.676, 117.583	18.213, 13.362	
	SD, SE	77.0160, 38.5080	16.3222, 6.1692	
	MEDIAN	119.442	14.286	
	MIN, MAX	58.056, 237.764	3.741, 52.000	
	5%, 95%	58.056, 237.764	3.741, 52.000	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	4	7	0.0107
	MEAN, GEO MEAN	132.262, 107.556	16.264, 12.155	
	SD, SE	95.8013, 47.9007	13.2303, 5.0006	
	MEDIAN	110.370	10.509	
	MIN, MAX	43.555, 264.754	3.693, 39.941	
	5%, 95%	43.555, 264.754	3.693, 39.941	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438519

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 156 of 264)

Biomarker: NNAL (pmol/mg Creatinine)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	4	7	0.0182
	MEAN, GEO MEAN	0.626, 0.453	0.068, 0.050	
	SD, SE	0.5487, 0.2743	0.0555, 0.0210	
	MEDIAN	0.485	0.036	
	MIN, MAX	0.139, 1.395	0.017, 0.154	
	5%, 95%	0.139, 1.395	0.017, 0.154	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	4	7	0.0107
	MEAN, GEO MEAN	0.639, 0.562	0.087, 0.064	
	SD, SE	0.3682, 0.1841	0.0782, 0.0296	
	MEDIAN	0.571	0.068	
	MIN, MAX	0.278, 1.137	0.018, 0.249	
	5%, 95%	0.278, 1.137	0.018, 0.249	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	4	7	0.0107
	MEAN, GEO MEAN	0.633, 0.515	0.078, 0.058	
	SD, SE	0.4579, 0.2289	0.0633, 0.0239	
	MEDIAN	0.528	0.050	
	MIN, MAX	0.209, 1.266	0.018, 0.191	
	5%, 95%	0.209, 1.266	0.018, 0.191	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 157 of 264)

Biomarker: NNAL ((pg/mg Creatinine)/cigarette per day)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	4		NA
	MEAN, GEO MEAN	10.392, 6.023		
	SD, SE	12.6764, 6.3382		
	MEDIAN	5.390		
	MIN, MAX	1.614, 29.174		
	5%, 95%	1.614, 29.174		
	# of BLQ/ALQ Values	0/0		
Week 3	N	4		NA
	MEAN, GEO MEAN	8.964, 7.143		
	SD, SE	7.4027, 3.7014		
	MEDIAN	6.409		
	MIN, MAX	3.225, 19.814		
	5%, 95%	3.225, 19.814		
	# of BLQ/ALQ Values	0/0		
Overall [*]	N	4		NA
	MEAN, GEO MEAN	9.679, 6.707		
	SD, SE	10.0346, 5.0173		
	MEDIAN	5.900		
	MIN, MAX	2.420, 24.494		
	5%, 95%	2.420, 24.494		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438521

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 158 of 264)

Biomarker: NNAL ((pmol/mg Creatinine)/cigarette per day)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	4		NA
	MEAN, GEO MEAN	0.050, 0.029		
	SD, SE	0.0607, 0.0304		
	MEDIAN	0.026		
	MIN, MAX	0.008, 0.140		
	5%, 95%	0.008, 0.140		
	# of BLQ/ALQ Values	0/0		
Week 3	N	4		NA
	MEAN, GEO MEAN	0.043, 0.034		
	SD, SE	0.0356, 0.0178		
	MEDIAN	0.031		
	MIN, MAX	0.015, 0.095		
	5%, 95%	0.015, 0.095		
	# of BLQ/ALQ Values	0/0		
Overall [†]	N	4		NA
	MEAN, GEO MEAN	0.047, 0.033		
	SD, SE	0.0482, 0.0241		
	MEDIAN	0.029		
	MIN, MAX	0.012, 0.118		
	5%, 95%	0.012, 0.118		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

[†] Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438522

Final Draft: 22 October 2003

Page 553 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 159 of 264)

Biomarker: NNAL (pg/mL)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	4	7	0.0031
	MEAN, GEO MEAN	122.8, 118.5	10.4, 10.4	
	SD, SE	38.17, 19.08	0.00, 0.00	
	MEDIAN	117.3	10.4	
	MIN, MAX	83.3, 173.3	10.4, 10.4	
	5%, 95%	83.3, 173.3	10.4, 10.4	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	4	7	0.0031
	MEAN, GEO MEAN	153.7, 127.2	10.4, 10.4	
	SD, SE	98.66, 49.33	0.00, 0.00	
	MEDIAN	142.5	10.4	
	MIN, MAX	46.0, 283.7	10.4, 10.4	
	5%, 95%	46.0, 283.7	10.4, 10.4	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	4	7	0.0031
	MEAN, GEO MEAN	138.2, 125.4	10.4, 10.4	
	SD, SE	68.33, 34.16	0.00, 0.00	
	MEDIAN	129.9	10.4	
	MIN, MAX	64.7, 228.5	10.4, 10.4	
	5%, 95%	64.7, 228.5	10.4, 10.4	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438523

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 160 of 264)

Biomarker: NNAL (pmol/L)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	4	7	0.0031
	MEAN, GEO MEAN	586.9, 566.3	49.7, 49.7	
	SD, SE	182.44, 91.22	0.00, 0.00	
	MEDIAN	560.5	49.7	
	MIN, MAX	398.2, 828.4	49.7, 49.7	
	5%, 95%	398.2, 828.4	49.7, 49.7	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	4	7	0.0031
	MEAN, GEO MEAN	734.5, 608.1	49.7, 49.7	
	SD, SE	471.57, 235.79	0.00, 0.00	
	MEDIAN	681.0	49.7	
	MIN, MAX	219.9, 1356.1	49.7, 49.7	
	5%, 95%	219.9, 1356.1	49.7, 49.7	
	# of BLQ/ALQ Values	0/0	7/0	
Overall [†]	N	4	7	0.0031
	MEAN, GEO MEAN	660.7, 599.2	49.7, 49.7	
	SD, SE	326.69, 163.35	0.00, 0.00	
	MEDIAN	620.7	49.7	
	MIN, MAX	309.1, 1092.3	49.7, 49.7	
	5%, 95%	309.1, 1092.3	49.7, 49.7	

* P-value from Wilcoxon rank-sum test.

† Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 161 of 264)

Biomarker: NNAL ((pg/mL)/cigarette per day)		Analytical Lab: INBIFO	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	4	
	MEAN, GEO MEAN	8.1, 7.5	
	SD, SE	3.51, 1.76	
	MEDIAN	7.5	
	MIN, MAX	4.6, 12.7	
	5%, 95%	4.6, 12.7	
	# of BLQ/ALQ Values	0/0	
Week 3	N	4	
	MEAN, GEO MEAN	9.4, 7.8	
	SD, SE	5.37, 2.69	
	MEDIAN	10.3	
	MIN, MAX	2.6, 14.2	
	5%, 95%	2.6, 14.2	
	# of BLQ/ALQ Values	0/0	
Overall*	N	4	
	MEAN, GEO MEAN	8.7, 7.8	
	SD, SE	4.27, 2.14	
	MEDIAN	9.2	
	MIN, MAX	3.6, 12.9	
	5%, 95%	3.6, 12.9	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438525

Final Draft: 22 October 2003

Page 556 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 162 of 264)

Biomarker: NNAL ((pmol/L)/cigarette per day)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	4		NA
	MEAN, GEO MEAN	38.6, 36.0		
	SD, SE	16.77, 8.38		
	MEDIAN	35.8		
	MIN, MAX	22.1, 60.8		
	5%, 95%	22.1, 60.8		
	# of BLQ/ALQ Values	0/0		
Week 3	N	4		NA
	MEAN, GEO MEAN	44.7, 36.9		
	SD, SE	25.76, 12.88		
	MEDIAN	49.3		
	MIN, MAX	12.2, 67.8		
	5%, 95%	12.2, 67.8		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	4		NA
	MEAN, GEO MEAN	41.7, 37.2		
	SD, SE	20.37, 10.18		
	MEDIAN	43.9		
	MIN, MAX	17.2, 61.8		
	5%, 95%	17.2, 61.8		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438526

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 163 of 264)

Biomarker: NNAL plus NNAL-gluc (pg/24hr)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	4	7	0.0107
	MEAN, GEO MEAN	549554.500, 462813.558	17892.457, 15800.916	
	SD, SE	293611.7770, 146805.8885	9736.3366, 3679.9893	
	MEDIAN	604996.500	12688.000	
	MIN, MAX	152850.000, 835375.000	8112.000, 33363.200	
	5%, 95%	152850.000, 835375.000	8112.000, 33363.200	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	4	8	0.0084
	MEAN, GEO MEAN	585318.250, 569775.116	23637.250, 21026.754	
	SD, SE	157681.1304, 78840.5652	12126.9421, 4287.5215	
	MEDIAN	566380.500	21580.000	
	MIN, MAX	413080.000, 795432.000	7800.000, 47762.000	
	5%, 95%	413080.000, 795432.000	7800.000, 47762.000	
	# of BLQ/ALQ Values	0/0	7/0	
Overall*	N	4	8	0.0085
	MEAN, GEO MEAN	567436.375, 535070.239	22631.700, 19764.230	
	SD, SE	191729.1352, 95864.5676	12789.3686, 4521.7246	
	MEDIAN	644308.500	19552.000	
	MIN, MAX	282965.000, 698163.500	7956.000, 47762.000	
	5%, 95%	282965.000, 698163.500	7956.000, 47762.000	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438527

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 164 of 264)

Biomarker: NNAL plus NNAL-gluc (pmol/24hr) Analytical Lab: INBIFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	4	7	0.0107
	MEAN, GEO MEAN	2626.871, 2212.249	85.526, 75.528	
	SD, SE	1403.4645, 701.7323	46.5396, 17.5903	
	MEDIAN	2891.884	60.649	
	MIN, MAX	730.623, 3993.093	38.775, 159.476	
	5%, 95%	730.623, 3993.093	38.775, 159.476	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	4	8	0.0084
	MEAN, GEO MEAN	2797.821, 2723.525	112.986, 100.508	
	SD, SE	753.7159, 376.8580	57.9667, 20.4943	
	MEDIAN	2707.299	103.153	
	MIN, MAX	1974.522, 3802.165	37.284, 228.302	
	5%, 95%	1974.522, 3802.165	37.284, 228.302	
	# of BLQ/ALQ Values	0/0	7/0	
Overall [†]	N	4	8	0.0085
	MEAN, GEO MEAN	2712.346, 2557.636	108.180, 94.473	
	SD, SE	916.4653, 458.2327	61.1329, 21.6138	
	MEDIAN	3079.795	93.459	
	MIN, MAX	1352.573, 3337.222	38.030, 228.302	
	5%, 95%	1352.573, 3337.222	38.030, 228.302	

* P-value from Wilcoxon rank-sum test.

[†] Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438528

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 165 of 264)

Biomarker: NNAL plus NNAL-gluc ((pg/24hr)/cigarette per day)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	4		NA
	MEAN, GEO MEAN	36071.731, 29425.119		
	SD, SE	19984.6413, 9992.3206		
	MEDIAN	41741.728		
	MIN, MAX	8491.667, 52311.800		
	5%, 95%	8491.667, 52311.800		
	# of BLQ/ALQ Values	0/0		
Week 3	N	4		NA
	MEAN, GEO MEAN	37705.629, 34611.491		
	SD, SE	19492.3489, 9746.1745		
	MEDIAN	30793.813		
	MIN, MAX	22948.889, 66286.000		
	5%, 95%	22948.889, 66286.000		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	4		NA
	MEAN, GEO MEAN	36888.680, 33129.734		
	SD, SE	18231.6861, 9115.8431		
	MEDIAN	36267.771		
	MIN, MAX	15720.278, 59298.900		
	5%, 95%	15720.278, 59298.900		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438529

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 166 of 264)

Biomarker: NNAL plus NNAL-gluc ((pmol/24hr)/cigarette per day)		Analytical Lab: INBIFO	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	4	
	MEAN, GEO MEAN	172.423, 140.652	
	SD, SE	95.5266, 47.7633	
	MEDIAN	199.526	
	MIN, MAX	40.590, 250.050	
	5%, 95%	40.590, 250.050	
Week 3	# of BLQ/ALQ Values	0/0	
	N	4	
	MEAN, GEO MEAN	180.233, 165.443	
	SD, SE	93.1733, 46.5867	
	MEDIAN	147.195	
	MIN, MAX	109.696, 316.847	
Overall*	5%, 95%	109.696, 316.847	
	# of BLQ/ALQ Values	0/0	
	N	4	
	MEAN, GEO MEAN	176.328, 158.360	
	SD, SE	87.1476, 43.5738	
	MEDIAN	173.361	
	MIN, MAX	75.143, 283.449	
	5%, 95%	75.143, 283.449	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.1.3-3
 Parameter Estimates for Biomarkers of Exposure with Half-Life Less Than or Equal to 3 Days
 Exposure-Response Modeling Results From NLIN Procedure
 (Page 5 of 10)

Biomarker	Unit	Parameter	Estimate	Standard Error	Quasi-Likelihood Ratio Test P-value
Cotinine	nmol/mg Creatinine	Intercept	-0.061131	0.4064676	0.8832
		Self-exposure	0.001643	0.0005350	0.0011
		Age	0.009740	0.0061555	0.1147
		Body Mass Index	-0.020746	0.0089445	0.0266
		Job Status	-0.443813	0.1656637	0.0043
		Servings High in Fat	-0.011072	0.0047884	0.0199
		Exposure to Cigarette Smoke From Spouse at Home	0.002641	0.0008547	<0.0001
		CYP1A2 Phenotyping	0.250673	0.1356350	0.0694

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 168 of 264)

Biomarker: NNAL plus NNAL-gluc (pmol/mg Creatinine)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	4	7	0.0107
	MEAN, GEO MEAN	2.104, 1.547	0.068, 0.050	
	SD, SE	1.4686, 0.7343	0.0555, 0.0210	
	MEDIAN	2.075	0.036	
	MIN, MAX	0.340, 3.928	0.017, 0.154	
	5%, 95%	0.340, 3.928	0.017, 0.154	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	4	8	0.0085
	MEAN, GEO MEAN	1.867, 1.724	0.092, 0.070	
	SD, SE	0.8925, 0.4462	0.0739, 0.0261	
	MEDIAN	1.631	0.076	
	MIN, MAX	1.084, 3.121	0.018, 0.249	
	5%, 95%	1.084, 3.121	0.018, 0.249	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	4	8	0.0085
	MEAN, GEO MEAN	1.986, 1.713	0.084, 0.064	
	SD, SE	1.1592, 0.5796	0.0612, 0.0217	
	MEDIAN	1.853	0.066	
	MIN, MAX	0.712, 3.525	0.018, 0.191	
	5%, 95%	0.712, 3.525	0.018, 0.191	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438532

Final Draft: 22 October 2003

Page 563 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 169 of 264)

Biomarker: NNAL plus NNAL-gluc ((pg/mg Creatinine)/cigarette per day) Analytical Lab: INBIFO			
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	4	
	MEAN, GEO MEAN	33.394, 20.575	
	SD, SE	33.9393, 16.9697	
	MEDIAN	23.723	
	MIN, MAX	3.951, 82.179	
	5%, 95%	3.951, 82.179	
	# of BLQ/ALQ Values	0/0	
Week 3	N	4	
	MEAN, GEO MEAN	25.939, 21.917	
	SD, SE	19.1954, 9.5977	
	MEDIAN	18.370	
	MIN, MAX	12.598, 54.418	
	5%, 95%	12.598, 54.418	
	# of BLQ/ALQ Values	0/0	
Overall*	N	4	
	MEAN, GEO MEAN	29.667, 22.351	
	SD, SE	26.4666, 13.2333	
	MEDIAN	21.047	
	MIN, MAX	8.275, 68.299	
	5%, 95%	8.275, 68.299	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438533

Final Draft: 22 October 2003

Page 564 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 170 of 264)

Biomarker: NNAL plus NNAL-gluc ((pmol/mg Creatinine)/cigarette per day)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	4		NA
	MEAN, GEO MEAN	0.160, 0.099		
	SD, SE	0.1622, 0.0811		
	MEDIAN	0.114		
	MIN, MAX	0.019, 0.393		
	5%, 95%	0.019, 0.393		
	# of BLQ/ALQ Values	0/0		
Week 3	N	4		NA
	MEAN, GEO MEAN	0.124, 0.104		
	SD, SE	0.0918, 0.0459		
	MEDIAN	0.088		
	MIN, MAX	0.060, 0.260		
	5%, 95%	0.060, 0.260		
	# of BLQ/ALQ Values	0/0		
Overall ^c	N	4		NA
	MEAN, GEO MEAN	0.142, 0.107		
	SD, SE	0.1267, 0.0633		
	MEDIAN	0.101		
	MIN, MAX	0.040, 0.327		
	5%, 95%	0.040, 0.327		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^c Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438534

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 171 of 264)

Biomarker: NNAL plus NNAL-gluc (pg/mL)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	4	7	0.0031
	MEAN, GEO MEAN	445.0, 404.7	10.4, 10.4	
	SD, SE	205.33, 102.66	0.00, 0.00	
	MEDIAN	453.9	10.4	
	MIN, MAX	203.8, 668.3	10.4, 10.4	
	5%, 95%	203.8, 668.3	10.4, 10.4	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	4	8	0.0033
	MEAN, GEO MEAN	444.2, 390.3	13.7, 12.2	
	SD, SE	251.04, 125.52	9.30, 3.29	
	MEDIAN	407.0	10.4	
	MIN, MAX	179.6, 783.3	10.4, 36.7	
	5%, 95%	179.6, 783.3	10.4, 36.7	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	4	8	0.0033
	MEAN, GEO MEAN	444.6, 403.5	13.7, 12.2	
	SD, SE	201.70, 100.85	9.30, 3.29	
	MEDIAN	460.2	10.4	
	MIN, MAX	191.7, 666.4	10.4, 36.7	
	5%, 95%	191.7, 666.4	10.4, 36.7	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 172 of 264)

Biomarker: NNAL plus NNAL-gluc (pmol/L)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	4	7	0.0031
	MEAN, GEO MEAN	2127.0, 1934.3	49.7, 49.7	
	SD, SE	981.45, 490.73	0.00, 0.00	
	MEDIAN	2169.7	49.7	
	MIN, MAX	974.2, 3194.5	49.7, 49.7	
	5%, 95%	974.2, 3194.5	49.7, 49.7	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	4	8	0.0033
	MEAN, GEO MEAN	2123.3, 1865.7	65.4, 58.2	
	SD, SE	1199.98, 599.99	44.44, 15.71	
	MEDIAN	1945.2	49.7	
	MIN, MAX	858.5, 3744.2	49.7, 175.4	
	5%, 95%	858.5, 3744.2	49.7, 175.4	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	4	8	0.0033
	MEAN, GEO MEAN	2125.2, 1928.8	65.4, 58.2	
	SD, SE	964.06, 482.03	44.44, 15.71	
	MEDIAN	2199.5	49.7	
	MIN, MAX	916.4, 3185.4	49.7, 175.4	
	5%, 95%	916.4, 3185.4	49.7, 175.4	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438536

Final Draft: 22 October 2003

Page 567 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 173 of 264)

Biomarker: NNAL plus NNAL-gluc ((pg/mL)/cigarette per day)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	4		NA
	MEAN, GEO MEAN	28.5, 25.7		
	SD, SE	12.47, 6.24		
	MEDIAN	31.7		
	MIN, MAX	11.3, 39.3		
	5%, 95%	11.3, 39.3		
	# of BLQ/ALQ Values	0/0		
Week 3	N	4		NA
	MEAN, GEO MEAN	26.9, 23.7		
	SD, SE	13.42, 6.71		
	MEDIAN	29.2		
	MIN, MAX	10.0, 39.2		
	5%, 95%	10.0, 39.2		
	# of BLQ/ALQ Values	0/0		
Overall*	N	4		NA
	MEAN, GEO MEAN	27.7, 25.1		
	SD, SE	11.53, 5.77		
	MEDIAN	32.2		
	MIN, MAX	10.7, 35.9		
	5%, 95%	10.7, 35.9		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 174 of 264)

Biomarker: NNAL plus NNAL-gluc ((pmol/L)/cigarette per day)		Analytical Lab: INBIFO	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	4	
	MEAN, GEO MEAN	136.2, 123.0	
	SD, SE	59.64, 29.82	
	MEDIAN	151.3	
	MIN, MAX	54.1, 187.9	
	5%, 95%	54.1, 187.9	
	# of BLQ/ALQ Values	0/0	
Week 3	N	4	
	MEAN, GEO MEAN	128.6, 113.3	
	SD, SE	64.12, 32.05	
	MEDIAN	139.8	
	MIN, MAX	47.7, 187.2	
	5%, 95%	47.7, 187.2	
	# of BLQ/ALQ Values	0/0	
Overall*	N	4	
	MEAN, GEO MEAN	132.4, 119.7	
	SD, SE	55.22, 27.61	
	MEDIAN	153.5	
	MIN, MAX	50.9, 171.8	
	5%, 95%	50.9, 171.8	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438538

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 175 of 264)

Biomarker: NNAL-O-glucuronide (pmol/L)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	4	7	0.0031
	MEAN, GEO MEAN	1540.2, 1323.6	0.0, NA	
	SD, SE	910.77, 455.39	0.00, 0.00	
	MEDIAN	1451.5	0.0	
	MIN, MAX	576.1, 2681.6	0.0, 0.0	
	5%, 95%	576.1, 2681.6	0.0, 0.0	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	4	7	0.0031
	MEAN, GEO MEAN	1388.9, 1249.1	0.0, NA	
	SD, SE	729.66, 364.83	0.00, 0.00	
	MEDIAN	1264.3	0.0	
	MIN, MAX	638.7, 2388.1	0.0, 0.0	
	5%, 95%	638.7, 2388.1	0.0, 0.0	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	4	7	0.0031
	MEAN, GEO MEAN	1464.5, 1315.6	0.0, NA	
	SD, SE	690.13, 345.06	0.00, 0.00	
	MEDIAN	1578.8	0.0	
	MIN, MAX	607.4, 2093.2	0.0, 0.0	
	5%, 95%	607.4, 2093.2	0.0, 0.0	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438539

Final Draft: 22 October 2003

Page 570 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 176 of 264)

Biomarker: NNAL-O-glucuronide ((pmol/L)/cigarette per day) Analytical Lab: INBIFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	4		NA
	MEAN, GEO MEAN	97.5, 84.1		
	SD, SE	52.09, 26.05		
	MEDIAN	100.2		
	MIN, MAX	32.0, 157.7		
	5%, 95%	32.0, 157.7		
	# of BLQ/ALQ Values	0/0		
Week 3	N	4		NA
	MEAN, GEO MEAN	84.0, 75.9		
	SD, SE	38.36, 19.18		
	MEDIAN	90.5		
	MIN, MAX	35.5, 119.4		
	5%, 95%	35.5, 119.4		
	# of BLQ/ALQ Values	0/0		
Overall*	N	4		NA
	MEAN, GEO MEAN	90.8, 81.7		
	SD, SE	38.20, 19.10		
	MEDIAN	107.4		
	MIN, MAX	33.8, 114.6		
	5%, 95%	33.8, 114.6		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 177 of 264)

Biomarker: NNAL-O-glucuronide (pmol/24hr)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	4	7	0.0031
	MEAN, GEO MEAN	1911.172, 1513.743	0.000, NA	
	SD, SE	1220.1075, 610.0537	0.0000, 0.0000	
	MEDIAN	1930.306	0.000	
	MIN, MAX	432.075, 3352.000	0.000, 0.000	
	5%, 95%	432.075, 3352.000	0.000, 0.000	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	4	7	0.0031
	MEAN, GEO MEAN	1853.886, 1823.438	0.000, NA	
	SD, SE	401.2446, 200.6223	0.0000, 0.0000	
	MEDIAN	1764.388	0.000	
	MIN, MAX	1469.010, 2417.760	0.000, 0.000	
	5%, 95%	1469.010, 2417.760	0.000, 0.000	
	# of BLQ/ALQ Values	0/0	7/0	
Overall*	N	4	7	0.0031
	MEAN, GEO MEAN	1882.529, 1770.202	0.000, NA	
	SD, SE	675.7396, 337.8698	0.0000, 0.0000	
	MEDIAN	2005.422	0.000	
	MIN, MAX	950.543, 2568.731	0.000, 0.000	
	5%, 95%	950.543, 2568.731	0.000, 0.000	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438541

Final Draft: 22 October 2003

Page 572 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 178 of 264)

Biomarker: NNAL-O-glucuronide ((pmol/24hr)/cigarette per day)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	4		NA
	MEAN, GEO MEAN	123.714, 96.242		
	SD, SE	75.0082, 37.5041		
	MEDIAN	136.837		
	MIN, MAX	24.004, 197.176		
	5%, 95%	24.004, 197.176		
	# of BLQ/ALQ Values	0/0		
Week 3	N	4		NA
	MEAN, GEO MEAN	118.821, 110.767		
	SD, SE	56.0040, 28.0020		
	MEDIAN	96.097		
	MIN, MAX	81.612, 201.480		
	5%, 95%	81.612, 201.480		
	# of BLQ/ALQ Values	0/0		
Overall†	N	4		NA
	MEAN, GEO MEAN	121.268, 109.622		
	SD, SE	56.7231, 28.3615		
	MEDIAN	125.440		
	MIN, MAX	52.808, 181.383		
	5%, 95%	52.808, 181.383		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

† Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438542

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 179 of 264)

Biomarker: NNAL-O-glucuronide (pmol/mg Creatinine)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	4	7	0.0031
	MEAN, GEO MEAN	1.479, 1.058	0.000, NA	
	SD, SE	0.9830, 0.4915	0.0000, 0.0000	
	MEDIAN	1.590	0.000	
	MIN, MAX	0.201, 2.534	0.000, 0.000	
	5%, 95%	0.201, 2.534	0.000, 0.000	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	4	7	0.0031
	MEAN, GEO MEAN	1.228, 1.155	0.000, NA	
	SD, SE	0.5275, 0.2638	0.0000, 0.0000	
	MEDIAN	1.061	0.000	
	MIN, MAX	0.806, 1.985	0.000, 0.000	
	5%, 95%	0.806, 1.985	0.000, 0.000	
	# of BLQ/ALQ Values	0/0	7/0	
Overall†	N	4	7	0.0031
	MEAN, GEO MEAN	1.354, 1.189	0.000, NA	
	SD, SE	0.7197, 0.3599	0.0000, 0.0000	
	MEDIAN	1.326	0.000	
	MIN, MAX	0.504, 2.260	0.000, 0.000	
	5%, 95%	0.504, 2.260	0.000, 0.000	

* P-value from Wilcoxon rank-sum test.

† Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as 1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438543

Final Draft: 22 October 2003

Page 574 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 180 of 264)

Biomarker: NNAL-O-glucuronide ((nmol/mg Creatinine)/cigarette per day) Analytical Lab: INBIFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	4		NA
	MEAN, GEO MEAN	0.110, 0.067		
	SD, SE	0.1034, 0.0517		
	MEDIAN	0.088		
	MIN, MAX	0.011, 0.253		
	5%, 95%	0.011, 0.253		
	# of BLQ/ALQ Values	0/0		
Week 3	N	4		NA
	MEAN, GEO MEAN	0.081, 0.070		
	SD, SE	0.0563, 0.0282		
	MEDIAN	0.057		
	MIN, MAX	0.045, 0.165		
	5%, 95%	0.045, 0.165		
	# of BLQ/ALQ Values	0/0		
Overall*	N	4		NA
	MEAN, GEO MEAN	0.096, 0.074		
	SD, SE	0.0789, 0.0395		
	MEDIAN	0.073		
	MIN, MAX	0.028, 0.209		
	5%, 95%	0.028, 0.209		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438544

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 181 of 264)

Biomarker: Nicotine (nmol/24hr)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6	3	0.0282
	MEAN, GEO MEAN	9618.834, 7479.916	7.072, 6.609	
	SD, SE	7409.9864, 3025.1143	3.0623, 1.7680	
	MEDIAN	6290.338	6.936	
	MIN, MAX	3259.536, 19895.897	4.080, 10.200	
	5%, 95%	3259.536, 19895.897	4.080, 10.200	
	# of BLQ/ALQ Values	0/0	3/0	
Week 2	N	6	2	0.0668
	MEAN, GEO MEAN	8208.238, 7076.088	7.548, 6.393	
	SD, SE	4490.9820, 1833.4357	5.6738, 4.0120	
	MEDIAN	8354.878	7.548	
	MIN, MAX	3484.431, 13388.466	3.536, 11.560	
	5%, 95%	3484.431, 13388.466	3.536, 11.560	
	# of BLQ/ALQ Values	0/0	2/0	
Week 3	N	5	4	0.0200
	MEAN, GEO MEAN	6005.220, 5280.694	7.076, 6.689	
	SD, SE	2926.7725, 1308.8925	2.7799, 1.3899	
	MEDIAN	7103.308	6.569	
	MIN, MAX	2126.580, 8844.885	4.284, 10.880	
	5%, 95%	2126.580, 8844.885	4.284, 10.880	
	# of BLQ/ALQ Values	0/0	4/0	
Overall*	N	6	6	0.0051
	MEAN, GEO MEAN	8471.514, 7224.185	8.359, 7.845	
	SD, SE	5060.2532, 2065.8397	2.9810, 1.2170	
	MEDIAN	7066.450	8.609	
	MIN, MAX	3555.830, 15498.722	3.967, 11.560	
	5%, 95%	3555.830, 15498.722	3.967, 11.560	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics).

PM3006438545

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 182 of 264)

Biomarker: Nicotine (µg/24hr)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	3	0.0282
	MEAN, GEO MEAN	1560.175, 1213.243	1.147, 1.072	
	SD, SE	1201.8996, 490.6734	0.4964, 0.2866	
	MEDIAN	1020.293	1.125	
	MIN, MAX	528.697, 3227.114	0.662, 1.654	
	5%, 95%	528.697, 3227.114	0.662, 1.654	
	# of BLQ/ALQ Values	0/0	3/0	
Week 2	N	6	2	0.0668
	MEAN, GEO MEAN	1331.376, 1147.742	1.225, 1.037	
	SD, SE	728.4371, 297.3832	0.9199, 0.6505	
	MEDIAN	1355.162	1.225	
	MIN, MAX	565.175, 2171.609	0.574, 1.875	
	5%, 95%	565.175, 2171.609	0.574, 1.875	
	# of BLQ/ALQ Values	0/0	2/0	
Week 3	N	5	4	0.0200
	MEAN, GEO MEAN	974.047, 856.528	1.148, 1.085	
	SD, SE	474.7226, 212.3024	0.4509, 0.2255	
	MEDIAN	1152.157	1.066	
	MIN, MAX	344.931, 1434.640	0.695, 1.765	
	5%, 95%	344.931, 1434.640	0.695, 1.765	
	# of BLQ/ALQ Values	0/0	4/0	
Overall ^b	N	6	6	0.0051
	MEAN, GEO MEAN	1374.080, 1171.763	1.356, 1.273	
	SD, SE	820.7730, 335.0792	0.4833, 0.1973	
	MEDIAN	1146.178	1.396	
	MIN, MAX	576.756, 2513.893	0.644, 1.875	
	5%, 95%	576.756, 2513.893	0.644, 1.875	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438546

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 183 of 264)

Biomarker: Nicotine ((nmol/24hr)/cigarette per day)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	636.191, 455.251		
	SD, SE	531.8371, 217.1216		
	MEDIAN	535.377		
	MIN, MAX	181.085, 1503.563		
	5%, 95%	181.085, 1503.563		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	765.869, 536.234		
	SD, SE	716.1272, 292.3577		
	MEDIAN	451.760		
	MIN, MAX	178.705, 2015.446		
	5%, 95%	178.705, 2015.446		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	618.861, 483.430		
	SD, SE	510.4448, 228.2779		
	MEDIAN	394.628		
	MIN, MAX	187.266, 1474.148		
	5%, 95%	187.266, 1474.148		
	# of BLQ/ALQ Values	0/0		
Overall [†]	N	6		NA
	MEAN, GEO MEAN	678.707, 553.168		
	SD, SE	433.9425, 177.1563		
	MEDIAN	612.633		
	MIN, MAX	221.461, 1239.200		
	5%, 95%	221.461, 1239.200		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

[†] Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438547

Final Draft: 22 October 2003

Page 578 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 184 of 264)

Biomarker: Nicotine ((µg/24hr)/cigarette per day) Analytical Lab: INBIFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6		NA
	MEAN, GEO MEAN	103.190, 73.842		
	SD, SE	85.2639, 35.2171		
	MEDIAN	86.839		
	MIN, MAX	29.372, 243.878		
	5%, 95%	29.372, 243.878		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	124.224, 85.977		
	SD, SE	116.1556, 47.4203		
	MEDIAN	73.276		
	MIN, MAX	28.986, 326.905		
	5%, 95%	28.986, 326.905		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	100.380, 78.413		
	SD, SE	82.7940, 37.0256		
	MEDIAN	64.009		
	MIN, MAX	30.375, 239.107		
	5%, 95%	30.375, 239.107		
	# of BLQ/ALQ Values	0/0		
Overall*	N	6		NA
	MEAN, GEO MEAN	110.087, 89.724		
	SD, SE	70.3855, 28.7347		
	MEDIAN	99.370		
	MIN, MAX	35.921, 200.998		
	5%, 95%	35.921, 200.998		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438548

Final Draft: 22 October 2003

Page 579 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 185 of 264)

Biomarker: Nicotine (nmol/mg Creatinine)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6	3	0.0275
	MEAN, GEO MEAN	6.631, 5.419	0.005, 0.005	
	SD, SE	4.3231, 1.7649	0.0006, 0.0003	
	MEDIAN	5.003	0.005	
	MIN, MAX	1.717, 12.677	0.004, 0.005	
	5%, 95%	1.717, 12.677	0.004, 0.005	
	# of BLQ/ALQ Values	0/0	3/0	
Week 2	N	6	2	0.0668
	MEAN, GEO MEAN	6.414, 5.576	0.008, 0.006	
	SD, SE	3.4787, 1.4202	0.0064, 0.0045	
	MEDIAN	6.483	0.008	
	MIN, MAX	2.159, 12.067	0.003, 0.012	
	5%, 95%	2.159, 12.067	0.003, 0.012	
	# of BLQ/ALQ Values	0/0	2/0	
Week 3	N	5	4	0.0200
	MEAN, GEO MEAN	5.449, 5.159	0.006, 0.005	
	SD, SE	2.0593, 0.9210	0.0024, 0.0012	
	MEDIAN	4.773	0.006	
	MIN, MAX	3.605, 8.447	0.003, 0.008	
	5%, 95%	3.605, 8.447	0.003, 0.008	
	# of BLQ/ALQ Values	0/0	4/0	
Overall*	N	6	6	0.0050
	MEAN, GEO MEAN	6.376, 5.742	0.006, 0.006	
	SD, SE	3.0639, 1.2508	0.0032, 0.0013	
	MEDIAN	5.903	0.005	
	MIN, MAX	2.883, 10.457	0.004, 0.012	
	5%, 95%	2.883, 10.457	0.004, 0.012	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438549

Final Draft: 22 October 2003

Page 580 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 186 of 264)

Biomarker: Nicotine (µg/mg Creatinine)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6	3	0.0256
	MEAN, GEO MEAN	1.076, 0.879	0.001, 0.001	
	SD, SE	0.7014, 0.2863	0.0000, 0.0000	
	MEDIAN	0.812	0.001	
	MIN, MAX	0.278, 2.056	0.001, 0.001	
	5%, 95%	0.278, 2.056	0.001, 0.001	
	# of BLQ/ALQ Values	0/0	3/0	
Week 2	N	6	2	0.0668
	MEAN, GEO MEAN	1.040, 0.904	0.001, NA	
	SD, SE	0.5642, 0.2303	0.0014, 0.0010	
	MEDIAN	1.052	0.001	
	MIN, MAX	0.350, 1.957	0.000, 0.002	
	5%, 95%	0.350, 1.957	0.000, 0.002	
	# of BLQ/ALQ Values	0/0	2/0	
Week 3	N	5	4	0.0179
	MEAN, GEO MEAN	0.884, 0.837	0.001, NA	
	SD, SE	0.3339, 0.1493	0.0005, 0.0003	
	MEDIAN	0.774	0.001	
	MIN, MAX	0.585, 1.370	0.000, 0.001	
	5%, 95%	0.585, 1.370	0.000, 0.001	
	# of BLQ/ALQ Values	0/0	4/0	
Overall ^b	N	6	6	0.0043
	MEAN, GEO MEAN	1.034, 0.931	0.001, NA	
	SD, SE	0.4971, 0.2029	0.0006, 0.0003	
	MEDIAN	0.958	0.001	
	MIN, MAX	0.467, 1.696	0.000, 0.002	
	5%, 95%	0.467, 1.696	0.000, 0.002	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438550

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 187 of 264)

Biomarker: Nicotine ((nmol/mg Creatinine)/cigarette per day) Analytical Lab: INBIFO				P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	0.455, 0.329		
	SD, SE	0.3700, 0.1511		
	MEDIAN	0.360		
	MIN, MAX	0.095, 1.056		
	5%, 95%	0.095, 1.056		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	0.582, 0.423		
	SD, SE	0.4804, 0.1961		
	MEDIAN	0.364		
	MIN, MAX	0.108, 1.275		
	5%, 95%	0.108, 1.275		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	0.608, 0.472		
	SD, SE	0.4860, 0.2173		
	MEDIAN	0.552		
	MIN, MAX	0.180, 1.408		
	5%, 95%	0.180, 1.408		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	6		NA
	MEAN, GEO MEAN	0.538, 0.442		
	SD, SE	0.3327, 0.1358		
	MEDIAN	0.495		
	MIN, MAX	0.155, 0.948		
	5%, 95%	0.155, 0.948		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438551

Final Draft: 22 October 2003

Page 582 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 188 of 264)

Biomarker: Nicotine ((µg/mg Creatinine)/cigarette per day)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	0.074, 0.053		
	SD, SE	0.0601, 0.0245		
	MEDIAN	0.059		
	MIN, MAX	0.015, 0.171		
	5%, 95%	0.015, 0.171		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	0.095, 0.069		
	SD, SE	0.0779, 0.0318		
	MEDIAN	0.059		
	MIN, MAX	0.018, 0.207		
	5%, 95%	0.018, 0.207		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	0.099, 0.077		
	SD, SE	0.0787, 0.0352		
	MEDIAN	0.090		
	MIN, MAX	0.029, 0.228		
	5%, 95%	0.029, 0.228		
	# of BLQ/ALQ Values	0/0		
Overall*	N	6		NA
	MEAN, GEO MEAN	0.087, 0.072		
	SD, SE	0.0540, 0.0220		
	MEDIAN	0.081		
	MIN, MAX	0.025, 0.154		
	5%, 95%	0.025, 0.154		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438552

Final Draft: 22 October 2003

Page 583 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 189 of 264)

Biomarker: Nicotine (nmol/L)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	3	0.0256
	MEAN, GEO MEAN	7197.1, 4444.0	3.4, 3.4	
	SD, SE	7757.37, 3166.93	0.00, 0.00	
	MEDIAN	3394.6	3.4	
	MIN, MAX	1356.6, 20738.8	3.4, 3.4	
	5%, 95%	1356.6, 20738.8	3.4, 3.4	
	# of BLQ/ALQ Values	0/0	3/0	
Week 2	N	6	2	0.0651
	MEAN, GEO MEAN	6056.4, 4199.7	3.4, 3.4	
	SD, SE	5389.15, 2200.11	0.00, 0.00	
	MEDIAN	3774.8	3.4	
	MIN, MAX	1805.1, 14396.2	3.4, 3.4	
	5%, 95%	1805.1, 14396.2	3.4, 3.4	
	# of BLQ/ALQ Values	0/0	2/0	
Week 3	N	5	4	0.0151
	MEAN, GEO MEAN	3400.4, 2972.7	3.4, 3.4	
	SD, SE	1754.96, 784.84	0.00, 0.00	
	MEDIAN	4113.9	3.4	
	MIN, MAX	1528.7, 5294.2	3.4, 3.4	
	5%, 95%	1528.7, 5294.2	3.4, 3.4	
	# of BLQ/ALQ Values	0/0	4/0	
Overall ^b	N	6	6	0.0028
	MEAN, GEO MEAN	6005.1, 4360.7	3.4, 3.4	
	SD, SE	5159.10, 2106.19	0.00, 0.00	
	MEDIAN	3513.2	3.4	
	MIN, MAX	1564.8, 13476.4	3.4, 3.4	
	5%, 95%	1564.8, 13476.4	3.4, 3.4	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438553

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 190 of 264)

Biomarker: Nicotine (ng/mL)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6	3	0.0256
	MEAN, GEO MEAN	1167.4, 720.8	0.6, 0.6	
	SD, SE	1258.24, 513.67	0.00, 0.00	
	MEDIAN	550.6	0.6	
	MIN, MAX	220.0, 3363.8	0.6, 0.6	
	5%, 95%	220.0, 3363.8	0.6, 0.6	
	# of BLQ/ALQ Values	0/0	3/0	
Week 2	N	6	2	0.0651
	MEAN, GEO MEAN	982.4, 681.2	0.6, 0.6	
	SD, SE	874.12, 356.86	0.00, 0.00	
	MEDIAN	612.3	0.6	
	MIN, MAX	292.8, 2335.1	0.6, 0.6	
	5%, 95%	292.8, 2335.1	0.6, 0.6	
	# of BLQ/ALQ Values	0/0	2/0	
Week 3	N	5	4	0.0151
	MEAN, GEO MEAN	551.6, 482.2	0.6, 0.6	
	SD, SE	284.63, 127.29	0.00, 0.00	
	MEDIAN	667.3	0.6	
	MIN, MAX	248.0, 858.7	0.6, 0.6	
	5%, 95%	248.0, 858.7	0.6, 0.6	
	# of BLQ/ALQ Values	0/0	4/0	
Overall†	N	6	6	0.0028
	MEAN, GEO MEAN	974.0, 707.3	0.6, 0.6	
	SD, SE	836.80, 341.62	0.00, 0.00	
	MEDIAN	569.9	0.6	
	MIN, MAX	253.8, 2185.9	0.6, 0.6	
	5%, 95%	253.8, 2185.9	0.6, 0.6	

* P-value from Wilcoxon rank-sum test.

† Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438554

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 191 of 264)

Biomarker: Nicotine ((nmol/L)/cigarette per day) Analytical Lab: INBIFO			
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	6	
	MEAN, GEO MEAN	525.7, 270.5	
	SD, SE	636.62, 259.90	
	MEDIAN	322.6	
	MIN, MAX	67.8, 1728.2	
	5%, 95%	67.8, 1728.2	
	# of BLQ/ALQ Values	0/0	
Week 2	N	6	
	MEAN, GEO MEAN	526.4, 318.3	
	SD, SE	504.53, 205.97	
	MEDIAN	365.7	
	MIN, MAX	90.3, 1308.7	
	5%, 95%	90.3, 1308.7	
	# of BLQ/ALQ Values	0/0	
Week 3	N	5	
	MEAN, GEO MEAN	342.3, 272.1	
	SD, SE	231.29, 103.44	
	MEDIAN	256.8	
	MIN, MAX	76.4, 685.7	
	5%, 95%	76.4, 685.7	
	# of BLQ/ALQ Values	0/0	
Overall*	N	6	
	MEAN, GEO MEAN	475.7, 337.9	
	SD, SE	389.64, 159.07	
	MEDIAN	447.2	
	MIN, MAX	78.2, 1159.4	
	5%, 95%	78.2, 1159.4	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438555

Final Draft: 22 October 2003

Page 586 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 192 of 264)

Biomarker: Nicotine ((ng/mL/cigarette per day) Analytical Lab: INBIFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6		NA
	MEAN, GEO MEAN	85.3, 43.9		
	SD, SE	103.25, 42.15		
	MEDIAN	52.3		
	MIN, MAX	11.0, 280.3		
	5%, 95%	11.0, 280.3		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	85.4, 51.6		
	SD, SE	81.86, 33.42		
	MEDIAN	59.3		
	MIN, MAX	14.6, 212.3		
	5%, 95%	14.6, 212.3		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	55.5, 44.2		
	SD, SE	37.50, 16.77		
	MEDIAN	41.7		
	MIN, MAX	12.4, 111.2		
	5%, 95%	12.4, 111.2		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	6		NA
	MEAN, GEO MEAN	77.2, 54.8		
	SD, SE	63.21, 25.81		
	MEDIAN	72.6		
	MIN, MAX	12.7, 188.1		
	5%, 95%	12.7, 188.1		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438556

Final Draft: 22 October 2003

Page 587 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 193 of 264)

Biomarker: Nicotine-N-glucuronide (nmol/L)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	2	0.0651
	MEAN, GEO MEAN	2601.8, 1698.4	9.3, 9.3	
	SD, SE	2910.33, 1188.14	0.00, 0.00	
	MEDIAN	1692.2	9.3	
	MIN, MAX	403.4, 8373.6	9.3, 9.3	
	5%, 95%	403.4, 8373.6	9.3, 9.3	
	# of BLQ/ALQ Values	0/0	2/0	
Week 2	N	6	2	0.0668
	MEAN, GEO MEAN	2877.9, 2365.5	27.7, 20.7	
	SD, SE	2171.62, 886.56	25.95, 18.35	
	MEDIAN	2040.6	27.7	
	MIN, MAX	1145.6, 6965.8	9.3, 46.0	
	5%, 95%	1145.6, 6965.8	9.3, 46.0	
	# of BLQ/ALQ Values	0/0	2/0	
Week 3	N	5	4	0.0151
	MEAN, GEO MEAN	1850.7, 1460.3	9.3, 9.3	
	SD, SE	1312.92, 587.16	0.00, 0.00	
	MEDIAN	1299.6	9.3	
	MIN, MAX	432.7, 3839.2	9.3, 9.3	
	5%, 95%	432.7, 3839.2	9.3, 9.3	
	# of BLQ/ALQ Values	0/0	4/0	
Overall ^b	N	6	6	0.0037
	MEAN, GEO MEAN	2495.4, 1962.5	11.3, 10.7	
	SD, SE	2051.46, 837.50	4.98, 2.03	
	MEDIAN	1908.5	9.3	
	MIN, MAX	797.4, 6392.9	9.3, 21.5	
	5%, 95%	797.4, 6392.9	9.3, 21.5	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234^a will be used as 1.234^a) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438557

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 194 of 264)

Biomarker: Nicotine-N-glucuronide ((nmol/L)/cigarette per day)		Analytical Lab: INBIFO	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	6	
	MEAN, GEO MEAN	175.8, 103.3	
	SD, SE	255.97, 104.50	
	MEDIAN	72.4	
	MIN, MAX	55.6, 697.8	
	5%, 95%	55.6, 697.8	
	# of BLQ/ALQ Values	0/0	
Week 2	N	6	
	MEAN, GEO MEAN	251.7, 179.3	
	SD, SE	223.92, 91.42	
	MEDIAN	165.8	
	MIN, MAX	57.3, 633.3	
	5%, 95%	57.3, 633.3	
	# of BLQ/ALQ Values	0/0	
Week 3	N	5	
	MEAN, GEO MEAN	185.7, 133.7	
	SD, SE	161.67, 72.30	
	MEDIAN	72.2	
	MIN, MAX	64.1, 400.1	
	5%, 95%	64.1, 400.1	
	# of BLQ/ALQ Values	0/0	
Overall*	N	6	
	MEAN, GEO MEAN	201.4, 145.3	
	SD, SE	190.41, 77.73	
	MEDIAN	115.5	
	MIN, MAX	59.0, 550.3	
	5%, 95%	59.0, 550.3	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438558

Final Draft: 22 October 2003

Page 589 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 195 of 264)

Biomarker: Nicotine-N-glucuronide (nmol/24hr)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6	2	0.0668
	MEAN, GEO MEAN	3721.249, 2858.728	19.530, 17.646	
	SD, SE	2425.2308, 990.0963	11.8370, 8.3700	
	MEDIAN	3264.808	19.530	
	MIN, MAX	548.624, 7285.032	11.160, 27.900	
	5%, 95%	548.624, 7285.032	11.160, 27.900	
	# of BLQ/ALQ Values	0/0	2/0	
Week 2	N	6	2	0.0668
	MEAN, GEO MEAN	4160.740, 3985.670	39.730, 38.893	
	SD, SE	1399.0642, 571.1656	11.4693, 8.1100	
	MEDIAN	3587.759	39.730	
	MIN, MAX	2816.360, 6478.194	31.620, 47.840	
	5%, 95%	2816.360, 6478.194	31.620, 47.840	
	# of BLQ/ALQ Values	0/0	2/0	
Week 3	N	5	4	0.0200
	MEAN, GEO MEAN	3377.796, 2594.128	19.353, 18.296	
	SD, SE	2201.0589, 984.3435	7.6038, 3.8019	
	MEDIAN	3139.430	17.968	
	MIN, MAX	597.126, 5950.760	11.718, 29.760	
	5%, 95%	597.126, 5950.760	11.718, 29.760	
	# of BLQ/ALQ Values	0/0	4/0	
Overall*	N	6	6	0.0051
	MEAN, GEO MEAN	3758.070, 3321.287	24.798, 24.160	
	SD, SE	1913.2244, 781.0706	5.9768, 2.4400	
	MEDIAN	3384.818	25.737	
	MIN, MAX	1320.703, 6571.329	16.740, 31.620	
	5%, 95%	1320.703, 6571.329	16.740, 31.620	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438559

Final Draft: 22 October 2003

Page 590 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 196 of 264)

Biomarker: Nicotine-N-glucuronide ((nmol/24hr)/cigarette per day)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	216.883, 173.991		
	SD, SE	193.3379, 78.9299		
	MEDIAN	152.465		
	MIN, MAX	91.437, 607.086		
	5%, 95%	91.437, 607.086		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	377.385, 302.039		
	SD, SE	290.7399, 118.6941		
	MEDIAN	231.422		
	MIN, MAX	163.182, 871.789		
	5%, 95%	163.182, 871.789		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	345.192, 237.484		
	SD, SE	330.7153, 147.9004		
	MEDIAN	156.972		
	MIN, MAX	99.521, 860.215		
	5%, 95%	99.521, 860.215		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	6		NA
	MEAN, GEO MEAN	303.001, 242.313		
	SD, SE	231.0965, 94.3447		
	MEDIAN	163.854		
	MIN, MAX	133.616, 635.179		
	5%, 95%	133.616, 635.179		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438560

Final Draft: 22 October 2003

Page 591 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 197 of 264)

Biomarker: Nicotine-N-glucuronide (nmol/mg Creatinine)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6	2	0.0668
	MEAN, GEO MEAN	2.750, 2.071	0.013, 0.012	
	SD, SE	1.8455, 0.7534	0.0021, 0.0015	
	MEDIAN	2.837	0.013	
	MIN, MAX	0.452, 5.118	0.011, 0.014	
	5%, 95%	0.452, 5.118	0.011, 0.014	
	# of BLQ/ALQ Values	0/0	2/0	
Week 2	N	6	2	0.0668
	MEAN, GEO MEAN	3.341, 3.141	0.036, 0.036	
	SD, SE	1.3634, 0.5566	0.0042, 0.0030	
	MEDIAN	3.126	0.036	
	MIN, MAX	1.972, 5.839	0.033, 0.039	
	5%, 95%	1.972, 5.839	0.033, 0.039	
	# of BLQ/ALQ Values	0/0	2/0	
Week 3	N	5	4	0.0200
	MEAN, GEO MEAN	3.039, 2.535	0.015, 0.014	
	SD, SE	1.8280, 0.8175	0.0059, 0.0029	
	MEDIAN	3.022	0.015	
	MIN, MAX	1.066, 4.929	0.009, 0.021	
	5%, 95%	1.066, 4.929	0.009, 0.021	
	# of BLQ/ALQ Values	0/0	4/0	
Overall*	N	6	6	0.0050
	MEAN, GEO MEAN	2.992, 2.662	0.019, 0.018	
	SD, SE	1.5386, 0.6281	0.0081, 0.0033	
	MEDIAN	2.800	0.020	
	MIN, MAX	1.486, 5.254	0.011, 0.033	
	5%, 95%	1.486, 5.254	0.011, 0.033	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438561

Final Draft: 22 October 2003

Page 592 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 198 of 264)

Biomarker: Nicotine-N-glyucuronide (nmol/mg Creatinine)/cigarette per day		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	0.161, 0.126		
	SD, SE	0.1384, 0.0565		
	MEDIAN	0.103		
	MIN, MAX	0.066, 0.427		
	5%, 95%	0.066, 0.427		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	0.296, 0.238		
	SD, SE	0.2022, 0.0826		
	MEDIAN	0.238		
	MIN, MAX	0.099, 0.552		
	5%, 95%	0.099, 0.552		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	0.325, 0.232		
	SD, SE	0.3027, 0.1354		
	MEDIAN	0.178		
	MIN, MAX	0.076, 0.822		
	5%, 95%	0.076, 0.822		
	# of BLQ/ALQ Values	0/0		
Overall*	N	6		NA
	MEAN, GEO MEAN	0.248, 0.196		
	SD, SE	0.1817, 0.0742		
	MEDIAN	0.178		
	MIN, MAX	0.080, 0.499		
	5%, 95%	0.080, 0.499		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438562

Final Draft; 22 October 2003

Page 593 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 199 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine) Analytical Lab: INBIFO

Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6	2	0.0668
	MEAN, GEO MEAN	51.700, 44.630	0.084, 0.078	
	SD, SE	29.5718, 12.0726	0.0403, 0.0285	
	MEDIAN	51.906	0.084	
	MIN, MAX	17.250, 102.868	0.055, 0.112	
	5%, 95%	17.250, 102.868	0.055, 0.112	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	6	3	0.0282
	MEAN, GEO MEAN	55.988, 49.589	0.071, 0.071	
	SD, SE	32.3685, 13.2144	0.0078, 0.0045	
	MEDIAN	50.322	0.075	
	MIN, MAX	28.075, 116.308	0.062, 0.076	
	5%, 95%	28.075, 116.308	0.062, 0.076	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	5	4	0.0200
	MEAN, GEO MEAN	49.089, 42.023	0.056, 0.053	
	SD, SE	29.2167, 13.0661	0.0193, 0.0096	
	MEDIAN	53.238	0.056	
	MIN, MAX	19.754, 92.206	0.036, 0.076	
	5%, 95%	19.754, 92.206	0.036, 0.076	
	# of BLQ/ALQ Values	0/0	0/0	
Overall*	N	6	5	0.0081
	MEAN, GEO MEAN	52.296, 45.973	0.067, 0.065	
	SD, SE	29.1763, 11.9112	0.0204, 0.0091	
	MEDIAN	51.240	0.072	
	MIN, MAX	21.693, 103.794	0.043, 0.094	
	5%, 95%	21.693, 103.794	0.043, 0.094	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438563

Final Draft: 22 October 2003

Page 594 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 200 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6		NA
	MEAN, GEO MEAN	3.034, 2.717		
	SD, SE	1.5673, 0.6399		
	MEDIAN	2.510		
	MIN, MAX	1.604, 5.143		
	5%, 95%	1.604, 5.143		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	4.436, 3.758		
	SD, SE	2.6207, 1.0699		
	MEDIAN	4.213		
	MIN, MAX	1.455, 8.410		
	5%, 95%	1.455, 8.410		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	4.559, 3.847		
	SD, SE	2.7668, 1.2374		
	MEDIAN	4.610		
	MIN, MAX	1.336, 8.873		
	5%, 95%	1.336, 8.873		
	# of BLQ/ALQ Values	0/0		
Overall ^a	N	6		NA
	MEAN, GEO MEAN	3.886, 3.448		
	SD, SE	1.8962, 0.7741		
	MEDIAN	4.010		
	MIN, MAX	1.465, 6.312		
	5%, 95%	1.465, 6.312		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438564

Final Draft: 22 October 2003

Page 595 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 201 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (mg/mg Creatinine) Analytical Lab: INBIFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6	2	0.0635
	MEAN, GEO MEAN	0.009, 0.007	0.000, NA	
	SD, SE	0.0048, 0.0020	0.0000, 0.0000	
	MEDIAN	0.009	0.000	
	MIN, MAX	0.003, 0.017	0.000, 0.000	
	5%, 95%	0.003, 0.017	0.000, 0.000	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	6	3	0.0243
	MEAN, GEO MEAN	0.009, 0.008	0.000, NA	
	SD, SE	0.0052, 0.0021	0.0000, 0.0000	
	MEDIAN	0.008	0.000	
	MIN, MAX	0.005, 0.019	0.000, 0.000	
	5%, 95%	0.005, 0.019	0.000, 0.000	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	5	4	0.0146
	MEAN, GEO MEAN	0.008, 0.007	0.000, NA	
	SD, SE	0.0048, 0.0021	0.0000, 0.0000	
	MEDIAN	0.009	0.000	
	MIN, MAX	0.003, 0.015	0.000, 0.000	
	5%, 95%	0.003, 0.015	0.000, 0.000	
	# of BLQ/ALQ Values	0/0	0/0	
Overall*	N	6	5	0.0055
	MEAN, GEO MEAN	0.009, 0.008	0.000, NA	
	SD, SE	0.0046, 0.0019	0.0000, 0.0000	
	MEDIAN	0.009	0.000	
	MIN, MAX	0.004, 0.017	0.000, 0.000	
	5%, 95%	0.004, 0.017	0.000, 0.000	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438565

Final Draft: 22 October 2003

Page 596 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 202 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites ((mg/mg Creatinine)/cigarette per day)		Analytical Lab: INBIFO	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	6	
	MEAN, GEO MEAN	0.000, NA	
	SD, SE	0.0005, 0.0002	
	MEDIAN	0.000	
	MIN, MAX	0.000, 0.001	
	5%, 95%	0.000, 0.001	
	# of BLQ/ALQ Values	0/0	
Week 2	N	6	
	MEAN, GEO MEAN	0.001, NA	
	SD, SE	0.0005, 0.0002	
	MEDIAN	0.001	
	MIN, MAX	0.000, 0.001	
	5%, 95%	0.000, 0.001	
	# of BLQ/ALQ Values	0/0	
Week 3	N	5	
	MEAN, GEO MEAN	0.001, NA	
	SD, SE	0.0004, 0.0002	
	MEDIAN	0.001	
	MIN, MAX	0.000, 0.001	
	5%, 95%	0.000, 0.001	
	# of BLQ/ALQ Values	0/0	
Overall*	N	6	
	MEAN, GEO MEAN	0.001, NA	
	SD, SE	0.0005, 0.0002	
	MEDIAN	0.001	
	MIN, MAX	0.000, 0.001	
	5%, 95%	0.000, 0.001	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438566

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 203 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (nmol/24hr)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6	2	0.0668
	MEAN, GEO MEAN	68080.876, 61601.687	79.565, 70.830	
	SD, SE	28039.2173, 10630.4660	51.2575, 36.2445	
	MEDIAN	79107.641	79.565	
	MIN, MAX	20949.848, 87412.052	43.320, 115.809	
	5%, 95%	20949.848, 87412.052	43.320, 115.809	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	6	3	0.0282
	MEAN, GEO MEAN	69068.865, 62930.735	94.730, 93.700	
	SD, SE	29783.4963, 12159.0614	16.4762, 9.5126	
	MEDIAN	72661.694	103.788	
	MIN, MAX	26881.034, 114295.450	75.712, 104.690	
	5%, 95%	26881.034, 114295.450	75.712, 104.690	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	5	4	0.0200
	MEAN, GEO MEAN	53596.816, 43011.516	72.417, 69.294	
	SD, SE	32272.5376, 14432.7176	24.6747, 12.3373	
	MEDIAN	55742.835	69.746	
	MIN, MAX	11067.738, 95783.485	45.486, 104.690	
	5%, 95%	11067.738, 95783.485	45.486, 104.690	
	# of BLQ/ALQ Values	0/0	0/0	
Overall ^b	N	6	5	0.0081
	MEAN, GEO MEAN	65164.772, 58044.148	81.764, 78.871	
	SD, SE	28150.9472, 11492.5761	24.3456, 10.8877	
	MEDIAN	71977.959	74.511	
	MIN, MAX	19632.873, 99062.755	54.839, 109.799	
	5%, 95%	19632.873, 99062.755	54.839, 109.799	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438567

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 204 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites ((nmol/24hr)/cigarette per day)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6		NA
	MEAN, GEO MEAN	3969.881, 3749.268		
	SD, SE	1552.3722, 633.7533		
	MEDIAN	3646.083		
	MIN, MAX	2318.472, 6808.809		
	5%, 95%	2318.472, 6808.809		
# of BLQ/ALQ Values		0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	5695.530, 4768.962		
	SD, SE	4031.7410, 1645.9514		
	MEDIAN	4776.254		
	MIN, MAX	2408.502, 13290.548		
	5%, 95%	2408.502, 13290.548		
# of BLQ/ALQ Values		0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	4742.508, 3937.563		
	SD, SE	3073.5371, 1374.5276		
	MEDIAN	4789.174		
	MIN, MAX	1844.623, 9290.473		
	5%, 95%	1844.623, 9290.473		
# of BLQ/ALQ Values		0/0		
Overall*	N	6		NA
	MEAN, GEO MEAN	4751.341, 4324.711		
	SD, SE	2249.8673, 918.5045		
	MEDIAN	4386.134		
	MIN, MAX	2480.448, 8299.831		
	5%, 95%	2480.448, 8299.831		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438568

Final Draft: 22 October 2003

Page 599 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2 1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 205 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (mg/24hr)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6	2	0.0668
	MEAN, GEO MEAN	11.045, 9.994	0.013, 0.012	
	SD, SE	4.2243, 1.7246	0.0085, 0.0060	
	MEDIAN	12.834	0.013	
	MIN, MAX	3.399, 14.181	0.007, 0.019	
	5%, 95%	3.399, 14.181	0.007, 0.019	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	6	3	0.0275
	MEAN, GEO MEAN	11.205, 10.209	0.015, 0.015	
	SD, SE	4.8317, 1.9725	0.0029, 0.0017	
	MEDIAN	11.788	0.017	
	MIN, MAX	4.361, 18.542	0.012, 0.017	
	5%, 95%	4.361, 18.542	0.012, 0.017	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	5	4	0.0200
	MEAN, GEO MEAN	8.695, 6.978	0.012, 0.011	
	SD, SE	5.2354, 2.3413	0.0041, 0.0021	
	MEDIAN	9.043	0.012	
	MIN, MAX	1.796, 15.539	0.007, 0.017	
	5%, 95%	1.796, 15.539	0.007, 0.017	
	# of BLQ/ALQ Values	0/0	0/0	
Overall*	N	6	5	0.0081
	MEAN, GEO MEAN	10.572, 9.417	0.013, 0.013	
	SD, SE	4.5670, 1.8645	0.0039, 0.0017	
	MEDIAN	11.677	0.012	
	MIN, MAX	3.185, 16.071	0.009, 0.018	
	5%, 95%	3.185, 16.071	0.009, 0.018	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438569

Final Draft: 22 October 2003

Page 600 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 206 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites ((mg/24hr)/cigarette per day)		Analytical Lab: INBIFO	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	6	
	MEAN, GEO MEAN	0.644, 0.608	
	SD, SE	0.2520, 0.1029	
	MEDIAN	0.592	
	MIN, MAX	0.376, 1.105	
	5%, 95%	0.376, 1.105	
	# of BLQ/ALQ Values	0/0	
Week 2	N	6	
	MEAN, GEO MEAN	0.924, 0.774	
	SD, SE	0.6539, 0.2670	
	MEDIAN	0.775	
	MIN, MAX	0.391, 2.156	
	5%, 95%	0.391, 2.156	
	# of BLQ/ALQ Values	0/0	
Week 3	N	5	
	MEAN, GEO MEAN	0.769, 0.639	
	SD, SE	0.4985, 0.2229	
	MEDIAN	0.777	
	MIN, MAX	0.299, 1.507	
	5%, 95%	0.299, 1.507	
	# of BLQ/ALQ Values	0/0	
Overall*	N	6	
	MEAN, GEO MEAN	0.771, 0.702	
	SD, SE	0.3647, 0.1489	
	MEDIAN	0.712	
	MIN, MAX	0.403, 1.346	
	5%, 95%	0.403, 1.346	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438570

Final Draft: 22 October 2003

Page 601 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 207 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (nmol/L)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6	2	0.0651
	MEAN, GEO MEAN	42916.1, 36598.8	36.1, 36.1	
	SD, SE	27913.02, 11395.44	0.00, 0.00	
	MEDIAN	31923.4	36.1	
	MIN, MAX	15404.3, 93914.6	36.1, 36.1	
	5%, 95%	15404.3, 93914.6	36.1, 36.1	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	6	3	0.0275
	MEAN, GEO MEAN	43564.7, 37349.6	48.3, 45.6	
	SD, SE	25097.21, 10245.89	21.19, 12.23	
	MEDIAN	36979.7	36.1	
	MIN, MAX	14851.4, 74519.1	36.1, 72.8	
	5%, 95%	14851.4, 74519.1	36.1, 72.8	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	5	4	0.0151
	MEAN, GEO MEAN	28148.3, 24212.6	36.1, 36.1	
	SD, SE	14484.66, 6477.74	0.00, 0.00	
	MEDIAN	25926.9	36.1	
	MIN, MAX	8020.1, 44901.7	36.1, 36.1	
	5%, 95%	8020.1, 44901.7	36.1, 36.1	
	# of BLQ/ALQ Values	0/0	0/0	
Overall*	N	6	5	0.0067
	MEAN, GEO MEAN	40224.0, 34606.9	38.5, 38.3	
	SD, SE	22647.85, 9245.95	5.46, 2.44	
	MEDIAN	33374.7	36.1	
	MIN, MAX	12758.6, 70848.7	36.1, 48.3	
	5%, 95%	12758.6, 70848.7	36.1, 48.3	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438571

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 208 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites ((nmol/L)/cigarette per day)		Analytical Lab: TNBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	2835.8, 2227.5		
	SD, SE	2513.94, 1026.31		
	MEDIAN	2086.4		
	MIN, MAX	946.3, 7826.2		
	5%, 95%	946.3, 7826.2		
Week 2	# of BLQ/ALQ Values	0/0		NA
	N	6		
	MEAN, GEO MEAN	3525.9, 2830.4		
	SD, SE	2429.59, 991.88		
	MEDIAN	2784.8		
	MIN, MAX	1216.4, 6702.7		
Week 3	5%, 95%	1216.4, 6702.7		NA
	# of BLQ/ALQ Values	0/0		
	N	5		
	MEAN, GEO MEAN	2524.2, 2216.6		
	SD, SE	1416.68, 633.56		
	MEDIAN	1954.8		
Overall ^b	MIN, MAX	1266.5, 4321.2		NA
	5%, 95%	1266.5, 4321.2		
	# of BLQ/ALQ Values	0/0		
	N	6		
	MEAN, GEO MEAN	2990.8, 2617.2		
	SD, SE	1768.98, 722.18		
	MEDIAN	2419.9		
	MIN, MAX	1431.7, 6090.2		
	5%, 95%	1431.7, 6090.2		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438572

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 209 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (mg/L)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	2	0.0651
	MEAN, GEO MEAN	7.0, 5.9	0.0, NA	
	SD, SE	4.51, 1.84	0.00, 0.00	
	MEDIAN	5.2	0.0	
	MIN, MAX	2.5, 15.2	0.0, 0.0	
	5%, 95%	2.5, 15.2	0.0, 0.0	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	6	3	0.0250
	MEAN, GEO MEAN	7.1, 6.0	0.0, NA	
	SD, SE	4.09, 1.67	0.00, 0.00	
	MEDIAN	6.0	0.0	
	MIN, MAX	2.4, 12.1	0.0, 0.0	
	5%, 95%	2.4, 12.1	0.0, 0.0	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	5	4	0.0151
	MEAN, GEO MEAN	4.6, 3.9	0.0, NA	
	SD, SE	2.38, 1.05	0.00, 0.00	
	MEDIAN	4.2	0.0	
	MIN, MAX	1.3, 7.3	0.0, 0.0	
	5%, 95%	1.3, 7.3	0.0, 0.0	
	# of BLQ/ALQ Values	0/0	0/0	
Overall ^b	N	6	5	0.0055
	MEAN, GEO MEAN	6.5, 5.6	0.0, NA	
	SD, SE	3.68, 1.50	0.00, 0.00	
	MEDIAN	5.4	0.0	
	MIN, MAX	2.1, 11.5	0.0, 0.0	
	5%, 95%	2.1, 11.5	0.0, 0.0	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 210 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites ((mg/L)/cigarette per day)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	0.5, 0.4		
	SD, SE	0.42, 0.17		
	MEDIAN	0.4		
	MIN, MAX	0.2, 1.3		
	5%, 95%	0.2, 1.3		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	0.6, 0.4		
	SD, SE	0.40, 0.16		
	MEDIAN	0.5		
	MIN, MAX	0.2, 1.1		
	5%, 95%	0.2, 1.1		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	0.4, 0.3		
	SD, SE	0.23, 0.10		
	MEDIAN	0.3		
	MIN, MAX	0.2, 0.7		
	5%, 95%	0.2, 0.7		
	# of BLQ/ALQ Values	0/0		
Overall*	N	6		NA
	MEAN, GEO MEAN	0.5, 0.4		
	SD, SE	0.29, 0.12		
	MEDIAN	0.4		
	MIN, MAX	0.2, 1.0		
	5%, 95%	0.2, 1.0		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438574

Final Draft: 22 October 2003

Page 605 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 211 of 264)

Biomarker: Total 3-hydroxycotinine (nmol/24hr) Analytical Lab: INBIFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	5	0.0081
	MEAN, GEO MEAN	33201.994, 29446.306	54.413, 41.136	
	SD, SE	16443.9553, 6713.2166	46.9354, 20.9901	
	MEDIAN	32778.032	39.779	
	MIN, MAX	11447.120, 59281.220	14.880, 132.925	
	5%, 95%	11447.120, 59281.220	14.880, 132.925	
	# of BLQ/ALQ Values	0/0	3/0	
Week 2	N	6	5	0.0081
	MEAN, GEO MEAN	34757.115, 29644.668	35.146, 29.986	
	SD, SE	23109.7163, 9434.5022	22.0406, 9.8569	
	MEDIAN	28940.034	35.650	
	MIN, MAX	13685.048, 78161.850	12.896, 70.392	
	5%, 95%	13685.048, 78161.850	12.896, 70.392	
	# of BLQ/ALQ Values	0/0	4/0	
Week 3	N	5	5	0.0122
	MEAN, GEO MEAN	25853.932, 18736.622	27.836, 26.364	
	SD, SE	24683.2568, 11038.6880	9.8852, 4.4208	
	MEDIAN	16042.225	25.394	
	MIN, MAX	5906.262, 68488.280	15.624, 39.680	
	5%, 95%	5906.262, 68488.280	15.624, 39.680	
	# of BLQ/ALQ Values	0/0	5/0	
Overall ^b	N	6	6	0.0051
	MEAN, GEO MEAN	32056.944, 27264.865	49.377, 38.249	
	SD, SE	20295.1308, 8285.4525	42.9212, 17.5225	
	MEDIAN	25715.951	37.165	
	MTN, MAX	10346.143, 68643.783	14.467, 132.925	
	5%, 95%	10346.143, 68643.783	14.467, 132.925	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438575

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 212 of 264)

Biomarker: Total 3-hydroxycotinine (µg/24hr)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6	5	0.0081
	MEAN, GEO MEAN	6381.423, 5659.580	10.458, 7.907	
	SD, SE	3160.5282, 1290.2802	9.0208, 4.0342	
	MEDIAN	6299.938	7.646	
	MIN, MAX	2200.136, 11393.850	2.860, 25.548	
	5%, 95%	2200.136, 11393.850	2.860, 25.548	
	# of BLQ/ALQ Values	0/0	3/0	
Week 2	N	6	5	0.0081
	MEAN, GEO MEAN	6680.318, 5697.705	6.755, 5.764	
	SD, SE	4441.6877, 1813.3114	4.2360, 1.8944	
	MEDIAN	5562.275	6.852	
	MIN, MAX	2630.266, 15022.708	2.479, 13.529	
	5%, 95%	2630.266, 15022.708	2.479, 13.529	
	# of BLQ/ALQ Values	0/0	4/0	
Week 3	N	5	5	0.0122
	MEAN, GEO MEAN	4969.126, 3601.179	5.350, 5.067	
	SD, SE	4744.1216, 2121.6357	1.8999, 0.8496	
	MEDIAN	3083.316	4.919	
	MIN, MAX	1135.184, 13163.447	3.003, 7.626	
	5%, 95%	1135.184, 13163.447	3.003, 7.626	
	# of BLQ/ALQ Values	0/0	5/0	
Overall*	N	6	6	0.0051
	MEAN, GEO MEAN	6161.345, 5240.307	9.490, 7.352	
	SD, SE	3900.7240, 1592.4639	8.2493, 3.3678	
	MEDIAN	4942.606	7.144	
	MIN, MAX	1988.529, 13193.335	2.781, 25.548	
	5%, 95%	1988.529, 13193.335	2.781, 25.548	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438576

Final Draft: 22 October 2003

Page 607 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 213 of 264)

Biomarker: Total 3-hydroxycotinine ((nmol/24hr)/cigarette per day)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	1886.926, 1792.193		
	SD, SE	639.6634, 261.1415		
	MEDIAN	1852.551		
	MIN, MAX	954.045, 2964.061		
	5%, 95%	954.045, 2964.061		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	2638.142, 2246.506		
	SD, SE	1731.2715, 706.7886		
	MEDIAN	1879.397		
	MIN, MAX	1222.808, 5570.650		
	5%, 95%	1222.808, 5570.650		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	1981.395, 1715.276		
	SD, SE	1106.5131, 494.8477		
	MEDIAN	2001.295		
	MIN, MAX	823.186, 3424.414		
	5%, 95%	823.186, 3424.414		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	6		NA
	MEAN, GEO MEAN	2162.396, 2023.888		
	SD, SE	879.8664, 359.2039		
	MEDIAN	1871.419		
	MIN, MAX	1312.972, 3432.189		
	5%, 95%	1312.972, 3432.189		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438577

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 214 of 264)

Biomarker: Total 3-hydroxycotinine ((μ g/24hr)/cigarette per day)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	362.667, 344.459		
	SD, SE	122.9436, 50.1915		
	MEDIAN	356.061		
	MIN, MAX	183.367, 569.693		
	5%, 95%	183.367, 569.693		
	# of BLQ/ALQ Values	0/0		
Week 2	N	5		NA
	MEAN, GEO MEAN	507.051, 431.779		
	SD, SE	332.7503, 135.8447		
	MEDIAN	361.220		
	MIN, MAX	235.024, 1070.679		
	5%, 95%	235.024, 1070.679		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	380.824, 329.676		
	SD, SE	212.6719, 95.1097		
	MEDIAN	384.649		
	MIN, MAX	158.216, 658.172		
	5%, 95%	158.216, 658.172		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	6		NA
	MEAN, GEO MEAN	415.613, 388.991		
	SD, SE	169.1105, 69.0391		
	MEDIAN	359.687		
	MIN, MAX	252.353, 659.667		
	5%, 95%	252.353, 659.667		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438578

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 215 of 264)

Biomarker: Total 3-hydroxycotinine (nmol/mg Creatinine)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6	5	0.0080
	MEAN, GEO MEAN	26.386, 21.334	0.040, 0.032	
	SD, SE	21.9570, 8.9639	0.0326, 0.0146	
	MEDIAN	20.188	0.025	
	MIN, MAX	9.426, 70.006	0.019, 0.096	
	5%, 95%	9.426, 70.006	0.019, 0.096	
	# of BLQ/ALQ Values	0/0	3/0	
Week 2	N	6	5	0.0075
	MEAN, GEO MEAN	28.860, 23.360	0.021, 0.020	
	SD, SE	25.1708, 10.2759	0.0073, 0.0032	
	MEDIAN	19.587	0.026	
	MIN, MAX	14.293, 79.538	0.011, 0.026	
	5%, 95%	14.293, 79.538	0.011, 0.026	
	# of BLQ/ALQ Values	0/0	4/0	
Week 3	N	5	5	0.0122
	MEAN, GEO MEAN	24.228, 18.306	0.021, 0.020	
	SD, SE	23.6263, 10.5660	0.0070, 0.0031	
	MEDIAN	15.321	0.023	
	MIN, MAX	9.955, 65.930	0.012, 0.028	
	5%, 95%	9.955, 65.930	0.012, 0.028	
	# of BLQ/ALQ Values	0/0	5/0	
Overall ^b	N	6	6	0.0051
	MEAN, GEO MEAN	26.496, 21.465	0.035, 0.028	
	SD, SE	22.6461, 9.2452	0.0306, 0.0125	
	MEDIAN	18.599	0.024	
	MIN, MAX	11.420, 71.825	0.014, 0.096	
	5%, 95%	11.420, 71.825	0.014, 0.096	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438579

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 216 of 264)

Biomarker: Total 3-hydroxycotinine (µg/mg Creatinine)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6	5	0.0080
	MEAN, GEO MEAN	5.071, 4.100	0.008, 0.006	
	SD, SE	4.2201, 1.7228	0.0059, 0.0027	
	MEDIAN	3.880	0.005	
	MIN, MAX	1.812, 13.455	0.004, 0.018	
	5%, 95%	1.812, 13.455	0.004, 0.018	
	# of BLQ/ALQ Values	0/0	3/0	
Week 2	N	6	5	0.0075
	MEAN, GEO MEAN	5.547, 4.490	0.004, 0.004	
	SD, SE	4.8377, 1.9750	0.0014, 0.0006	
	MEDIAN	3.765	0.005	
	MIN, MAX	2.747, 15.287	0.002, 0.005	
	5%, 95%	2.747, 15.287	0.002, 0.005	
	# of BLQ/ALQ Values	0/0	4/0	
Week 3	N	5	5	0.0119
	MEAN, GEO MEAN	4.657, 3.518	0.004, 0.004	
	SD, SE	4.5411, 2.0309	0.0013, 0.0006	
	MEDIAN	2.943	0.004	
	MIN, MAX	1.913, 12.672	0.002, 0.005	
	5%, 95%	1.913, 12.672	0.002, 0.005	
	# of BLQ/ALQ Values	0/0	5/0	
Overall*	N	6	6	0.0051
	MEAN, GEO MEAN	5.093, 4.126	0.007, 0.005	
	SD, SE	4.3527, 1.7770	0.0056, 0.0023	
	MEDIAN	3.575	0.005	
	MIN, MAX	2.195, 13.805	0.003, 0.018	
	5%, 95%	2.195, 13.805	0.003, 0.018	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438580

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 217 of 264)

Biomarker: Total 3-hydroxycotinine ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	1.505, 1.298		
	SD, SE	1.0220, 0.4172		
	MEDIAN	1.142		
	MIN, MAX	0.680, 3.500		
	5%, 95%	0.680, 3.500		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	2.096, 1.770		
	SD, SE	1.3236, 0.5404		
	MEDIAN	1.534		
	MIN, MAX	0.739, 3.977		
	5%, 95%	0.739, 3.977		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	1.955, 1.676		
	SD, SE	1.0343, 0.4626		
	MEDIAN	1.757		
	MIN, MAX	0.553, 3.297		
	5%, 95%	0.553, 3.297		
	# of BLQ/ALQ Values	0/0		
Overall*	N	6		NA
	MEAN, GEO MEAN	1.807, 1.601		
	SD, SE	1.0054, 0.4104		
	MEDIAN	1.548		
	MIN, MAX	0.763, 3.591		
	5%, 95%	0.763, 3.591		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438581

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 218 of 264)

Biomarker: Total 3-hydroxycotinine ((ug/mg Creatinine)/cigarette per day) Analytical Lab: INBIFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6		NA
	MEAN, GEO MEAN	0.290, 0.250		
	SD, SE	0.1964, 0.0802		
	MEDIAN	0.220		
	MIN, MAX	0.131, 0.673		
	5%, 95%	0.131, 0.673		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	0.403, 0.340		
	SD, SE	0.2544, 0.1038		
	MEDIAN	0.295		
	MIN, MAX	0.142, 0.764		
	5%, 95%	0.142, 0.764		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	0.376, 0.322		
	SD, SE	0.1990, 0.0890		
	MEDIAN	0.338		
	MIN, MAX	0.106, 0.634		
	5%, 95%	0.106, 0.634		
	# of BLQ/ALQ Values	0/0		
Overall*	N	6		NA
	MEAN, GEO MEAN	0.347, 0.308		
	SD, SE	0.1931, 0.0788		
	MEDIAN	0.298		
	MIN, MAX	0.147, 0.690		
	5%, 95%	0.147, 0.690		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438582

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 219 of 264)

Biomarker: Total 3-hydroxycotinine (nmol/L)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	5	0.0075
	MEAN, GEO MEAN	18760.8, 17494.6	24.5, 20.3	
	SD, SE	6817.90, 2783.39	16.64, 7.44	
	MEDIAN	20361.6	12.4	
	MIN, MAX	8417.0, 25578.5	12.4, 44.5	
	5%, 95%	8417.0, 25578.5	12.4, 44.5	
	# of BLQ/ALQ Values	0/0	3/0	
Week 2	N	6	5	0.0067
	MEAN, GEO MEAN	19977.0, 17594.2	18.3, 15.8	
	SD, SE	10727.64, 4379.54	13.19, 5.90	
	MEDIAN	18523.4	12.4	
	MIN, MAX	7560.8, 37689.3	12.4, 41.9	
	5%, 95%	7560.8, 37689.3	12.4, 41.9	
	# of BLQ/ALQ Values	0/0	4/0	
Week 3	N	5	5	0.0075
	MEAN, GEO MEAN	12925.5, 10547.5	12.4, 12.4	
	SD, SE	9343.85, 4178.70	0.00, 0.00	
	MEDIAN	9437.8	12.4	
	MIN, MAX	4279.9, 27954.4	12.4, 12.4	
	5%, 95%	4279.9, 27954.4	12.4, 12.4	
	# of BLQ/ALQ Values	0/0	5/0	
Overall ^b	N	6	6	0.0043
	MEAN, GEO MEAN	18260.5, 16211.6	20.6, 17.8	
	SD, SE	9101.47, 3715.66	12.90, 5.27	
	MEDIAN	17343.5	12.4	
	MIN, MAX	6752.6, 31633.9	12.4, 40.9	
	5%, 95%	6752.6, 31633.9	12.4, 40.9	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234^a will be used as 1.234^a) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438583

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 220 of 264)

Biomarker: Total 3-hydroxycotinine (ng/mL)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	5	0.0075
	MEAN, GEO MEAN	3605.8, 3362.4	4.7, 3.9	
	SD, SE	1310.43, 534.98	3.21, 1.44	
	MEDIAN	3913.5	2.4	
	MIN, MAX	1617.7, 4916.2	2.4, 8.6	
	5%, 95%	1617.7, 4916.2	2.4, 8.6	
	# of BLQ/ALQ Values	0/0	3/0	
Week 2	N	6	5	0.0067
	MEAN, GEO MEAN	3839.6, 3381.6	3.5, 3.1	
	SD, SE	2061.85, 841.75	2.55, 1.14	
	MEDIAN	3560.2	2.4	
	MIN, MAX	1453.2, 7243.9	2.4, 8.1	
	5%, 95%	1453.2, 7243.9	2.4, 8.1	
	# of BLQ/ALQ Values	0/0	4/0	
Week 3	N	5	5	0.0075
	MEAN, GEO MEAN	2484.3, 2027.2	2.4, 2.4	
	SD, SE	1795.88, 803.14	0.00, 0.00	
	MEDIAN	1813.9	2.4	
	MIN, MAX	822.6, 5372.8	2.4, 2.4	
	5%, 95%	822.6, 5372.8	2.4, 2.4	
	# of BLQ/ALQ Values	0/0	5/0	
Overall ^b	N	6	6	0.0043
	MEAN, GEO MEAN	3509.7, 3115.9	4.0, 3.4	
	SD, SE	1749.33, 714.16	2.50, 1.02	
	MEDIAN	3333.4	2.4	
	MIN, MAX	1297.8, 6080.1	2.4, 7.9	
	5%, 95%	1297.8, 6080.1	2.4, 7.9	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438584

Final Draft: 22 October 2003

Page 615 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 221 of 264)

Biomarker: Total 3-hydroxycotinine (nmol/L/cigarette per day)		Analytical Lab: INBIFO	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	6	
	MEAN, GEO MEAN	1189.4, 1064.8	
	SD, SE	551.72, 225.24	
	MEDIAN	1119.4	
	MIN, MAX	389.4, 2083.0	
	5%, 95%	389.4, 2083.0	
	# of BLQ/ALQ Values	0/0	
Week 2	N	6	
	MEAN, GEO MEAN	1510.8, 1333.3	
	SD, SE	765.95, 312.70	
	MEDIAN	1572.6	
	MIN, MAX	617.6, 2591.0	
	5%, 95%	617.6, 2591.0	
	# of BLQ/ALQ Values	0/0	
Week 3	N	5	
	MEAN, GEO MEAN	1034.0, 965.6	
	SD, SE	388.91, 173.93	
	MEDIAN	1243.6	
	MIN, MAX	524.3, 1397.7	
	5%, 95%	524.3, 1397.7	
	# of BLQ/ALQ Values	0/0	
Overall*	N	6	
	MEAN, GEO MEAN	1270.5, 1221.9	
	SD, SE	371.77, 151.78	
	MEDIAN	1317.4	
	MIN, MAX	756.2, 1776.3	
	5%, 95%	756.2, 1776.3	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438585

Final Draft: 22 October 2003

Page 616 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 222 of 264)

Biomarker: Total 3-hydroxycotinine ((ng/mL)/cigarette per day)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	228.6, 204.6		
	SD, SE	106.07, 43.30		
	MEDIAN	215.2		
	MIN, MAX	74.8, 400.4		
	5%, 95%	74.8, 400.4		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	290.4, 256.3		
	SD, SE	147.23, 60.10		
	MEDIAN	302.3		
	MIN, MAX	118.7, 498.0		
	5%, 95%	118.7, 498.0		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	198.7, 185.6		
	SD, SE	74.73, 33.42		
	MEDIAN	239.0		
	MIN, MAX	100.8, 268.6		
	5%, 95%	100.8, 268.6		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	6		NA
	MEAN, GEO MEAN	244.2, 234.9		
	SD, SE	71.44, 29.17		
	MEDIAN	253.2		
	MIN, MAX	145.4, 341.4		
	5%, 95%	145.4, 341.4		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438586

Final Draft: 22 October 2003

Page 617 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 223 of 264)

Biomarker: Total Cotinine (nmol/24hr)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6	6	0.0051
	MEAN, GEO MEAN	21538.800, 17732.715	22473, 20.850	
	SD, SE	11226.8961, 4583.3611	9.6010, 3.9196	
	MEDIAN	21849.563	19.360	
	MIN, MAX	3897.624, 34631.742	13.200, 35.288	
	5%, 95%	3897.624, 34631.742	13.200, 35.288	
Week 2	# of BLQ/ALQ Values	0/0	0/0	0.0034
	N	6	7	
	MEAN, GEO MEAN	21942.772, 19820.873	25.654, 23.904	
	SD, SE	8654.5985, 3533.2251	9.4756, 3.5815	
	MEDIAN	25091.510	30.250	
	MIN, MAX	6895.195, 28995.975	11.440, 37.400	
Week 3	5%, 95%	6895.195, 28995.975	11.440, 37.400	0.0058
	# of BLQ/ALQ Values	0/0	7/0	
	N	5	7	
	MEAN, GEO MEAN	18359.870, 13658.400	22446, 21.506	
	SD, SE	11454.7088, 5122.7015	7.1197, 2.6910	
	MEDIAN	20410.460	20.680	
Overall*	MIN, MAX	2437.770, 31425.320	13.860, 32.010	0.0024
	5%, 95%	2437.770, 31425.320	13.860, 32.010	
	# of BLQ/ALQ Values	0/0	7/0	
	N	6	8	
	MEAN, GEO MEAN	20878.245, 17708.653	23.599, 22.442	
	SD, SE	9961.1819, 4066.6355	7.6547, 2.7064	
Overall*	MEDIAN	22902.038	23.467	0.0024
	MIN, MAX	4410.196, 31587.791	12.833, 33.457	
	5%, 95%	4410.196, 31587.791	12.833, 33.457	
	# of BLQ/ALQ Values	0/0	7/0	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438587

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 224 of 264)

Biomarker: Total Cotinine (ug/24hr) Analytical Lab: INBIFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6	6	0.0051
	MEAN, GEO MEAN	3795.136, 3124.504	3.960, 3.674	
	SD, SE	1978.1792, 807.5883	1.6917, 0.6906	
	MEDIAN	3849.893	3.412	
	MIN, MAX	686.761, 6102.113	2.326, 6.218	
	5%, 95%	686.761, 6102.113	2.326, 6.218	
	# of BLQ/ALQ Values	0/0	6/0	
Week 2	N	6	7	0.0034
	MEAN, GEO MEAN	3866.317, 3492.438	4.520, 4.212	
	SD, SE	1524.9404, 622.5543	1.6696, 0.6310	
	MEDIAN	4421.124	5.330	
	MIN, MAX	1214.933, 5109.091	2.016, 6.590	
	5%, 95%	1214.933, 5109.091	2.016, 6.590	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	5	7	0.0058
	MEAN, GEO MEAN	3235.009, 2406.610	3.955, 3.789	
	SD, SE	2018.3196, 902.6199	1.2543, 0.4742	
	MEDIAN	3596.323	3.644	
	MIN, MAX	429.535, 5537.141	2.442, 5.640	
	5%, 95%	429.535, 5537.141	2.442, 5.640	
	# of BLQ/ALQ Values	0/0	7/0	
Overall*	N	6	8	0.0024
	MEAN, GEO MEAN	3678.747, 3120.264	4.158, 3.954	
	SD, SE	1755.1605, 716.5413	1.3489, 0.4769	
	MEDIAN	4035.339	4.135	
	MIN, MAX	777.076, 5565.769	2.261, 5.895	
	5%, 95%	777.076, 5565.769	2.261, 5.895	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438588

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 225 of 264)

Biomarker: Total Cotinine ((nmol/24hr)/cigarette per day)		Analytical Lab: INBIFO	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	6	
	MEAN, GEO MEAN	1229.881, 1079.267	
	SD, SE	823.2641, 336.0961	
	MEDIAN	982.101	
	MIN, MAX	649.604, 2885.979	
	5%, 95%	649.604, 2885.979	
	# of BLQ/ALQ Values	0/0	
Week 2	N	6	
	MEAN, GEO MEAN	1914.135, 1502.048	
	SD, SE	1583.3261, 646.3902	
	MEDIAN	1254.576	
	MIN, MAX	689.520, 4832.663	
	5%, 95%	689.520, 4832.663	
	# of BLQ/ALQ Values	0/0	
Week 3	N	5	
	MEAN, GEO MEAN	1797.060, 1250.382	
	SD, SE	1634.6604, 731.0423	
	MEDIAN	1020.523	
	MIN, MAX	406.295, 4282.406	
	5%, 95%	406.295, 4282.406	
	# of BLQ/ALQ Values	0/0	
Overall*	N	6	
	MEAN, GEO MEAN	1607.238, 1310.722	
	SD, SE	1140.8004, 465.7298	
	MEDIAN	1107.553	
	MIN, MAX	581.806, 3359.319	
	5%, 95%	581.806, 3359.319	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438589

Final Draft: 22 October 2003

Page 620 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 226 of 264)

Biomarker: Total Cotinine ((μ g/24hr)/cigarette per day)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	216.705, 190.167		
	SD, SE	145.0589, 59.2201		
	MEDIAN	173.047		
	MIN, MAX	114.460, 508.509		
	5%, 95%	114.460, 508.509		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	337.270, 264.661		
	SD, SE	278.9821, 113.8939		
	MEDIAN	221.056		
	MIN, MAX	121.493, 851.515		
	5%, 95%	121.493, 851.515		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	316.642, 220.317		
	SD, SE	288.0272, 128.8097		
	MEDIAN	179.816		
	MIN, MAX	71.589, 754.560		
	5%, 95%	71.589, 754.560		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	6		NA
	MEAN, GEO MEAN	283.195, 230.949		
	SD, SE	201.0090, 82.0616		
	MEDIAN	195.151		
	MIN, MAX	102.514, 591.912		
	5%, 95%	102.514, 591.912		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438590

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 227 of 264)

Biomarker: Total Cotinine (nmol/mg Creatinine) Analytical Lab: INBIFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	6	0.0050
	MEAN, GEO MEAN	15.933, 12.847	0.016, 0.014	
	SD, SE	9.1696, 3.7435	0.0098, 0.0040	
	MEDIAN	17.813	0.015	
	MIN, MAX	3.209, 24.408	0.006, 0.034	
	5%, 95%	3.209, 24.408	0.006, 0.034	
	# of BLQ/ALQ Values	0/0	6/0	
Week 2	N	6	7	0.0034
	MEAN, GEO MEAN	17.374, 15.619	0.018, 0.016	
	SD, SE	8.1799, 3.3394	0.0107, 0.0041	
	MEDIAN	16.762	0.014	
	MIN, MAX	7.201, 27.449	0.007, 0.038	
	5%, 95%	7.201, 27.449	0.007, 0.038	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	5	7	0.0056
	MEAN, GEO MEAN	16.373, 13.344	0.018, 0.017	
	SD, SE	9.6689, 4.3241	0.0051, 0.0019	
	MEDIAN	19.648	0.021	
	MIN, MAX	4.351, 25.375	0.011, 0.023	
	5%, 95%	4.351, 25.375	0.011, 0.023	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	6	8	0.0024
	MEAN, GEO MEAN	16.432, 14.120	0.019, 0.018	
	SD, SE	8.4653, 3.4559	0.0077, 0.0027	
	MEDIAN	17.962	0.018	
	MIN, MAX	4.920, 25.193	0.009, 0.030	
	5%, 95%	4.920, 25.193	0.009, 0.030	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438591

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 228 of 264)

Biomarker: Total Cotinine (µg/mg Creatinine)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	6	0.0049
	MEAN, GEO MEAN	2.807, 2.263	0.003, 0.002	
	SD, SE	1.6159, 0.6597	0.0017, 0.0007	
	MEDIAN	3.139	0.003	
	MIN, MAX	0.565, 4.301	0.001, 0.006	
	5%, 95%	0.565, 4.301	0.001, 0.006	
	# of BLQ/ALQ Values	0/0	6/0	
Week 2	N	6	7	0.0032
	MEAN, GEO MEAN	3.061, 2.752	0.003, 0.003	
	SD, SE	1.4415, 0.5885	0.0020, 0.0008	
	MEDIAN	2.954	0.002	
	MIN, MAX	1.269, 4.837	0.001, 0.007	
	5%, 95%	1.269, 4.837	0.001, 0.007	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	5	7	0.0046
	MEAN, GEO MEAN	2.885, 2.352	0.003, 0.003	
	SD, SE	1.7035, 0.7618	0.0011, 0.0004	
	MEDIAN	3.462	0.004	
	MIN, MAX	0.767, 4.471	0.002, 0.004	
	5%, 95%	0.767, 4.471	0.002, 0.004	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	6	8	0.0024
	MEAN, GEO MEAN	2.896, 2.488	0.003, 0.003	
	SD, SE	1.4915, 0.6089	0.0017, 0.0006	
	MEDIAN	3.165	0.003	
	MIN, MAX	0.867, 4.439	0.001, 0.006	
	5%, 95%	0.867, 4.439	0.001, 0.006	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438592

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 229 of 264)

Biomarker: Total Cotinine ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: INBIFO	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	6	
	MEAN, GEO MEAN	0.913, 0.782	
	SD, SE	0.6117, 0.2497	
	MEDIAN	0.626	
	MIN, MAX	0.446, 2.028	
	5%, 95%	0.446, 2.028	
	# of BLQ/ALQ Values	0/0	
Week 2	N	6	
	MEAN, GEO MEAN	1.462, 1.184	
	SD, SE	1.0294, 0.4203	
	MEDIAN	1.068	
	MIN, MAX	0.510, 3.058	
	5%, 95%	0.510, 3.058	
	# of BLQ/ALQ Values	0/0	
Week 3	N	5	
	MEAN, GEO MEAN	1.671, 1.222	
	SD, SE	1.4941, 0.6682	
	MEDIAN	0.982	
	MIN, MAX	0.442, 4.090	
	5%, 95%	0.442, 4.090	
	# of BLQ/ALQ Values	0/0	
Overall*	N	6	
	MEAN, GEO MEAN	1.293, 1.054	
	SD, SE	0.8934, 0.3647	
	MEDIAN	0.927	
	MIN, MAX	0.466, 2.611	
	5%, 95%	0.466, 2.611	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438593

Final Draft: 22 October 2003

Page 624 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 230 of 264)

Biomarker: Total Cotinine ((µg/mg Creatinine)/cigarette per day)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	0.161, 0.138		
	SD, SE	0.1076, 0.0439		
	MEDIAN	0.111		
	MIN, MAX	0.079, 0.357		
	5%, 95%	0.079, 0.357		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	0.258, 0.209		
	SD, SE	0.1813, 0.0740		
	MEDIAN	0.188		
	MIN, MAX	0.090, 0.539		
	5%, 95%	0.090, 0.539		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	0.295, 0.215		
	SD, SE	0.2634, 0.1178		
	MEDIAN	0.173		
	MIN, MAX	0.078, 0.721		
	5%, 95%	0.078, 0.721		
	# of BLQ/ALQ Values	0/0		
Overall*	N	6		NA
	MEAN, GEO MEAN	0.228, 0.186		
	SD, SE	0.1573, 0.0642		
	MEDIAN	0.164		
	MIN, MAX	0.082, 0.460		
	5%, 95%	0.082, 0.460		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438594

Final Draft: 22 October 2003

Page 625 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 231 of 264)

Biomarker: Total Cotinine (nmol/L) Analytical Lab: INBIFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6	6	0.0028
	MEAN, GEO MEAN	14356.4, 10535.4	11.0, 11.0	
	SD, SE	13129.60, 5360.14	0.00, 0.00	
	MEDIAN	11017.2	11.0	
	MIN, MAX	2865.9, 39806.6	11.0, 11.0	
	5%, 95%	2865.9, 39806.6	11.0, 11.0	
	# of BLQ/ALQ Values	0/0	6/0	
Week 2	N	6	7	0.0015
	MEAN, GEO MEAN	14653.4, 11763.7	11.0, 11.0	
	SD, SE	10167.85, 4151.01	0.00, 0.00	
	MEDIAN	11093.9	11.0	
	MIN, MAX	3809.5, 30867.0	11.0, 11.0	
	5%, 95%	3809.5, 30867.0	11.0, 11.0	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	5	7	0.0021
	MEAN, GEO MEAN	9971.7, 7888.8	11.0, 11.0	
	SD, SE	6819.34, 3049.70	0.00, 0.00	
	MEDIAN	8330.8	11.0	
	MIN, MAX	1766.5, 20274.4	11.0, 11.0	
	5%, 95%	1766.5, 20274.4	11.0, 11.0	
	# of BLQ/ALQ Values	0/0	7/0	
Overall*	N	6	8	0.0008
	MEAN, GEO MEAN	13463.2, 10521.5	11.0, 11.0	
	SD, SE	9773.22, 3989.90	0.00, 0.00	
	MEDIAN	10588.5	11.0	
	MIN, MAX	2814.0, 30316.0	11.0, 11.0	
	5%, 95%	2814.0, 30316.0	11.0, 11.0	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438595

Final Draft: 22 October 2003

Page 626 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 232 of 264)

Biomarker: Total Cotinine (ng/mL) Analytical Lab: INBiFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6	6	0.0028
	MEAN, GEO MEAN	2529.6, 1856.3	1.9, 1.9	
	SD, SE	2313.43, 944.45	0.00, 0.00	
	MEDIAN	1941.2	1.9	
	MIN, MAX	505.0, 7013.9	1.9, 1.9	
	5%, 95%	505.0, 7013.9	1.9, 1.9	
	# of BLQ/ALQ Values	0/0	6/0	
Week 2	N	6	7	0.0015
	MEAN, GEO MEAN	2581.9, 2072.8	1.9, 1.9	
	SD, SE	1791.59, 731.41	0.00, 0.00	
	MEDIAN	1954.8	1.9	
	MIN, MAX	671.2, 5438.8	1.9, 1.9	
	5%, 95%	671.2, 5438.8	1.9, 1.9	
	# of BLQ/ALQ Values	0/0	7/0	
Week 3	N	5	7	0.0021
	MEAN, GEO MEAN	1757.0, 1354.8	1.9, 1.9	
	SD, SE	1201.54, 537.34	0.00, 0.00	
	MEDIAN	1467.9	1.9	
	MIN, MAX	311.3, 3572.3	1.9, 1.9	
	5%, 95%	311.3, 3572.3	1.9, 1.9	
	# of BLQ/ALQ Values	0/0	7/0	
Overall*	N	6	8	0.0008
	MEAN, GEO MEAN	2372.2, 1853.9	1.9, 1.9	
	SD, SE	1722.05, 703.03	0.00, 0.00	
	MEDIAN	1865.7	1.9	
	MIN, MAX	495.8, 5341.7	1.9, 1.9	
	5%, 95%	495.8, 5341.7	1.9, 1.9	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 233 of 264)

Biomarker: Total Cotinine ((nmol/L)/cigarette per day)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	945.0, 641.2		
	SD, SE	1165.85, 475.96		
	MEDIAN	490.7		
	MIN, MAX	356.4, 3317.2		
	5%, 95%	356.4, 3317.2		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	1237.2, 891.5		
	SD, SE	1051.58, 429.31		
	MEDIAN	780.9		
	MIN, MAX	381.0, 2806.1		
	5%, 95%	381.0, 2806.1		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	962.2, 703.9		
	SD, SE	810.58, 362.50		
	MEDIAN	418.7		
	MIN, MAX	294.4, 1991.8		
	5%, 95%	294.4, 1991.8		
	# of BLQ/ALQ Values	0/0		
Overall ^c	N	6		NA
	MEAN, GEO MEAN	1043.2, 790.8		
	SD, SE	884.68, 361.17		
	MEDIAN	661.9		
	MIN, MAX	384.4, 2604.3		
	5%, 95%	384.4, 2604.3		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^c Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234) will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438597

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 234 of 264)

Biomarker: Total Cotinine ((ng/mL)/cigarette per day)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	166.5, 113.0		
	SD, SE	205.43, 83.87		
	MEDIAN	86.5		
	MIN, MAX	62.8, 584.5		
	5%, 95%	62.8, 584.5		
Week 2	# of BLQ/ALQ Values	0/0		NA
	N	6		
	MEAN, GEO MEAN	218.0, 157.1		
	SD, SE	185.29, 75.64		
	MEDIAN	137.6		
	MIN, MAX	67.1, 494.4		
Week 3	5%, 95%	67.1, 494.4		NA
	# of BLQ/ALQ Values	0/0		
	N	5		
	MEAN, GEO MEAN	169.6, 124.1		
	SD, SE	142.83, 63.88		
	MEDIAN	73.8		
Overall*	MIN, MAX	51.9, 351.0		NA
	5%, 95%	51.9, 351.0		
	# of BLQ/ALQ Values	0/0		
	N	6		
	MEAN, GEO MEAN	183.8, 139.4		
	SD, SE	155.89, 63.64		
Overall*	MEDIAN	116.7		NA
	MIN, MAX	67.7, 458.9		
	5%, 95%	67.7, 458.9		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438598

Final Draft: 22 October 2003

Page 629 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 235 of 264)

Biomarker: Total Nicotine (nmol/24hr)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	3	0.0282
	MEAN, GEO MEAN	13340.083, 10943.435	31361, 28.707	
	SD, SE	8949.6828, 3653.6927	14.0233, 8.0963	
	MEDIAN	10205.028	38.100	
	MIN, MAX	5497.128, 25327.788	15.240, 40.742	
	5%, 95%	5497.128, 25327.788	15.240, 40.742	
	# of BLQ/ALQ Values	0/0	3/0	
Week 2	N	6	5	0.0081
	MEAN, GEO MEAN	12368.978, 11224.563	40.565, 40.139	
	SD, SE	5727.7162, 2338.3303	6.8172, 3.0487	
	MEDIAN	11942.637	36.830	
	MIN, MAX	6300.791, 19866.660	34.925, 51.376	
	5%, 95%	6300.791, 19866.660	34.925, 51.376	
	# of BLQ/ALQ Values	0/0	4/0	
Week 3	N	5	7	0.0058
	MEAN, GEO MEAN	9383.015, 8059.175	29.054, 27.748	
	SD, SE	4868.4540, 2177.2388	9.1357, 3.4530	
	MEDIAN	9143.680	26.213	
	MIN, MAX	2723.706, 14156.770	16.002, 40.640	
	5%, 95%	2723.706, 14156.770	16.002, 40.640	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	6	7	0.0034
	MEAN, GEO MEAN	12229.584, 10705.606	31.847, 31.289	
	SD, SE	6469.9832, 2641.3596	6.2904, 2.3775	
	MEDIAN	11297.326	33.528	
	MIN, MAX	4876.534, 19783.739	22.860, 39.298	
	5%, 95%	4876.534, 19783.739	22.860, 39.298	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438599

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 236 of 264)

Biomarker: Total Nicotine (µg/24hr) Analytical Lab: INBIFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6	3	0.0282
	MEAN, GEO MEAN	2163.761, 1775.025	5.087, 4.656	
	SD, SE	1451.6384, 592.6289	2.2743, 1.3132	
	MEDIAN	1655.256	6.180	
	MIN, MAX	891.634, 4108.167	2.472, 6.608	
	5%, 95%	891.634, 4108.167	2.472, 6.608	
	# of BLQ/ALQ Values	0/0	3/0	
Week 2	N	6	5	0.0081
	MEAN, GEO MEAN	2006.248, 1820.624	6.580, 6.511	
	SD, SE	929.0356, 379.2772	1.1057, 0.4945	
	MEDIAN	1937.096	5.974	
	MIN, MAX	1021.988, 3222.372	5.665, 8.333	
	5%, 95%	1021.988, 3222.372	5.665, 8.333	
	# of BLQ/ALQ Values	0/0	4/0	
Week 3	N	5	7	0.0058
	MEAN, GEO MEAN	1521.925, 1307.198	4.713, 4.501	
	SD, SE	789.6633, 353.1482	1.4816, 0.5600	
	MEDIAN	1483.105	4.252	
	MIN, MAX	441.785, 2296.228	2.596, 6.592	
	5%, 95%	441.785, 2296.228	2.596, 6.592	
	# of BLQ/ALQ Values	0/0	7/0	
Overall*	N	6	7	0.0034
	MEAN, GEO MEAN	1983.638, 1736.449	5.166, 5.075	
	SD, SE	1049.4312, 428.4285	1.0202, 0.3856	
	MEDIAN	1832.426	5.439	
	MIN, MAX	790.974, 3208.922	3.708, 6.374	
	5%, 95%	790.974, 3208.922	3.708, 6.374	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438600

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 237 of 264)

Biomarker: Total Nicotine ((nmol/24hr)/cigarette per day)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	853.074, 666.051		
	SD, SE	687.2070, 280.5511		
	MEDIAN	667.862		
	MIN, MAX	305.396, 2110.649		
	5%, 95%	305.396, 2110.649		
Week 2	# of BLQ/ALQ Values	0/0		NA
	N	6		
	MEAN, GEO MEAN	1143.254, 850.610		
	SD, SE	1002.1522, 409.1269		
	MEDIAN	683.182		
	MIN, MAX	341.887, 2887.235		
Week 3	5%, 95%	341.887, 2887.235		NA
	# of BLQ/ALQ Values	0/0		
	N	5		
	MEAN, GEO MEAN	964.053, 737.791		
	SD, SE	833.1631, 372.6019		
	MEDIAN	507.982		
Overall ^b	MIN, MAX	344.237, 2334.363		NA
	5%, 95%	344.237, 2334.363		
	# of BLQ/ALQ Values	0/0		
	N	6		
	MEAN, GEO MEAN	981.707, 808.034		
	SD, SE	652.4491, 266.3612		
	MEDIAN	772.619		
	MIN, MAX	385.088, 1874.379		
	5%, 95%	385.088, 1874.379		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438601

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 238 of 264)

Biomarker: Total Nicotine ((ug/24hr)/cigarette per day)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	138.369, 108.033		
	SD, SE	111.4649, 45.5054		
	MEDIAN	108.328		
	MIN, MAX	49.535, 342.347		
	5%, 95%	49.535, 342.347		
Week 2	# of BLQ/ALQ Values	0/0		NA
	N	6		
	MEAN, GEO MEAN	185.436, 137.969		
	SD, SE	162.5493, 66.3605		
	MEDIAN	110.812		
	MIN, MAX	55.454, 468.310		
Week 3	5%, 95%	55.454, 468.310		NA
	# of BLQ/ALQ Values	0/0		
	N	5		
	MEAN, GEO MEAN	156.369, 119.670		
	SD, SE	135.1391, 60.4361		
	MEDIAN	82.395		
Overall*	MIN, MAX	55.835, 378.634		NA
	5%, 95%	55.835, 378.634		
	# of BLQ/ALQ Values	0/0		
	N	6		
	MEAN, GEO MEAN	159.233, 131.063		
	SD, SE	105.8274, 43.2039		
Overall*	MEDIAN	125.319		NA
	MIN, MAX	62.461, 304.025		
	5%, 95%	62.461, 304.025		
	# of BLQ/ALQ Values	0/0		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438602

Final Draft: 22 October 2003

Page 633 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 239 of 264)

Biomarker: Total Nicotine (nmol/mg Creatinine) Analytical Lab: INBIFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6	3	0.0282
	MEAN, GEO MEAN	9.381, 7.928	0.024, 0.022	
	SD, SE	5.4803, 2.2373	0.0129, 0.0074	
	MEDIAN	8.947	0.019	
	MIN, MAX	2.896, 17.795	0.015, 0.039	
	5%, 95%	2.896, 17.795	0.015, 0.039	
	# of BLQ/ALQ Values	0/0	3/0	
Week 2	N	6	5	0.0081
	MEAN, GEO MEAN	9.755, 8.845	0.031, 0.029	
	SD, SE	4.6862, 1.9131	0.0118, 0.0053	
	MEDIAN	9.474	0.027	
	MIN, MAX	4.131, 17.906	0.016, 0.044	
	5%, 95%	4.131, 17.906	0.016, 0.044	
	# of BLQ/ALQ Values	0/0	4/0	
Week 3	N	5	7	0.0057
	MEAN, GEO MEAN	8.488, 7.874	0.021, 0.020	
	SD, SE	3.6972, 1.6534	0.0064, 0.0024	
	MEDIAN	6.628	0.024	
	MIN, MAX	4.861, 13.377	0.013, 0.029	
	5%, 95%	4.861, 13.377	0.013, 0.029	
	# of BLQ/ALQ Values	0/0	7/0	
Overall*	N	6	7	0.0034
	MEAN, GEO MEAN	9.367, 8.525	0.025, 0.024	
	SD, SE	4.2474, 1.7340	0.0072, 0.0027	
	MEDIAN	9.697	0.025	
	MIN, MAX	4.390, 15.711	0.015, 0.034	
	5%, 95%	4.390, 15.711	0.015, 0.034	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438603

Final Draft: 22 October 2003

Page 634 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 240 of 264)

Biomarker: Total Nicotine (µg/mg Creatinine)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	5	3	0.0282
	MEAN, GEO MEAN	1.522, 1.286	0.004, 0.003	
	SD, SE	0.8887, 0.3628	0.0021, 0.0012	
	MEDIAN	1.451	0.003	
	MIN, MAX	0.470, 2.886	0.002, 0.006	
	5%, 95%	0.470, 2.886	0.002, 0.006	
	# of BLQ/ALQ Values	0/0	3/0	
Week 2	N	6	5	0.0078
	MEAN, GEO MEAN	1.582, 1.434	0.005, 0.005	
	SD, SE	0.7601, 0.3103	0.0019, 0.0008	
	MEDIAN	1.537	0.004	
	MIN, MAX	0.670, 2.904	0.003, 0.007	
	5%, 95%	0.670, 2.904	0.003, 0.007	
	# of BLQ/ALQ Values	0/0	4/0	
Week 3	N	5	7	0.0053
	MEAN, GEO MEAN	1.377, 1.277	0.003, 0.003	
	SD, SE	0.5999, 0.2683	0.0011, 0.0004	
	MEDIAN	1.075	0.004	
	MIN, MAX	0.788, 2.170	0.002, 0.005	
	5%, 95%	0.788, 2.170	0.002, 0.005	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	6	7	0.0032
	MEAN, GEO MEAN	1.519, 1.383	0.004, 0.004	
	SD, SE	0.6888, 0.2812	0.0013, 0.0005	
	MEDIAN	1.573	0.004	
	MIN, MAX	0.712, 2.548	0.002, 0.006	
	5%, 95%	0.712, 2.548	0.002, 0.006	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438604

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 241 of 264)

Biomarker: Total Nicotine ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: INBIFO	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	6	
	MEAN, GEO MEAN	0.615, 0.483	
	SD, SE	0.4755, 0.1941	
	MEDIAN	0.496	
	MIN, MAX	0.161, 1.483	
	5%, 95%	0.161, 1.483	
	# of BLQ/ALQ Values	0/0	
Week 2	N	6	
	MEAN, GEO MEAN	0.878, 0.670	
	SD, SE	0.5766, 0.2762	
	MEDIAN	0.570	
	MIN, MAX	0.207, 1.827	
	5%, 95%	0.207, 1.827	
	# of BLQ/ALQ Values	0/0	
Week 3	N	5	
	MEAN, GEO MEAN	0.933, 0.721	
	SD, SE	0.7763, 0.3472	
	MEDIAN	0.810	
	MIN, MAX	0.331, 2.230	
	5%, 95%	0.331, 2.230	
	# of BLQ/ALQ Values	0/0	
Overall*	N	6	
	MEAN, GEO MEAN	0.786, 0.648	
	SD, SE	0.5055, 0.2064	
	MEDIAN	0.636	
	MIN, MAX	0.236, 1.448	
	5%, 95%	0.236, 1.448	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438605

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 242 of 264)

Biomarker: Total Nicotine ((µg/mg Creatinine)/cigarette per day)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	0.100, 0.078		
	SD, SE	0.0774, 0.0316		
	MEDIAN	0.081		
	MIN, MAX	0.026, 0.241		
	5%, 95%	0.026, 0.241		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	0.143, 0.109		
	SD, SE	0.1095, 0.0447		
	MEDIAN	0.093		
	MIN, MAX	0.034, 0.296		
	5%, 95%	0.034, 0.296		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	0.151, 0.117		
	SD, SE	0.1261, 0.0564		
	MEDIAN	0.131		
	MIN, MAX	0.054, 0.362		
	5%, 95%	0.054, 0.362		
	# of BLQ/ALQ Values	0/0		
Overall*	N	6		NA
	MEAN, GEO MEAN	0.128, 0.105		
	SD, SE	0.0822, 0.0335		
	MEDIAN	0.103		
	MIN, MAX	0.038, 0.235		
	5%, 95%	0.038, 0.235		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438606

Final Draft: 22 October 2003

Page 637 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 243 of 264)

Biomarker: Total Nicotine (nmol/L) Analytical Lab: INBIFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	3	0.0256
	MEAN, GEO MEAN	9798.9, 6501.7	12.7, 12.7	
	SD, SE	10412.65, 4250.94	0.00, 0.00	
	MEDIAN	4765.0	12.7	
	MIN, MAX	2468.7, 29112.4	12.7, 12.7	
	5%, 95%	2468.7, 29112.4	12.7, 12.7	
	# of BLQ/ALQ Values	0/0	3/0	
Week 2	N	6	5	0.0067
	MEAN, GEO MEAN	8934.2, 6661.8	20.0, 16.7	
	SD, SE	7476.72, 3052.36	16.41, 7.34	
	MEDIAN	5769.3	12.7	
	MIN, MAX	2954.7, 21362.0	12.7, 49.4	
	5%, 95%	2954.7, 21362.0	12.7, 49.4	
	# of BLQ/ALQ Values	0/0	4/0	
Week 3	N	5	7	0.0021
	MEAN, GEO MEAN	5251.1, 4536.8	12.7, 12.7	
	SD, SE	2902.43, 1298.01	0.00, 0.00	
	MEDIAN	5824.0	12.7	
	MIN, MAX	1973.7, 9133.4	12.7, 12.7	
	5%, 95%	1973.7, 9133.4	12.7, 12.7	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	6	7	0.0021
	MEAN, GEO MEAN	8500.5, 6413.7	14.4, 14.0	
	SD, SE	7026.29, 2868.47	4.61, 1.74	
	MEDIAN	5421.7	12.7	
	MIN, MAX	2744.5, 19869.3	12.7, 24.9	
	5%, 95%	2744.5, 19869.3	12.7, 24.9	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438607

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 244 of 264)

Biomarker: Total Nicotine (ng/mL) Analytical Lab: INBIFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	3	0.0256
	MEAN, GEO MEAN	1589.4, 1054.6	2.1, 2.1	
	SD, SE	1688.92, 689.50	0.00, 0.00	
	MEDIAN	772.9	2.1	
	MIN, MAX	400.4, 4722.0	2.1, 2.1	
	5%, 95%	400.4, 4722.0	2.1, 2.1	
	# of BLQ/ALQ Values	0/0	3/0	
Week 2	N	6	5	0.0067
	MEAN, GEO MEAN	1449.1, 1080.5	3.3, 2.7	
	SD, SE	1212.72, 495.09	2.64, 1.18	
	MEDIAN	935.8	2.1	
	MIN, MAX	479.3, 3464.9	2.1, 8.0	
	5%, 95%	479.3, 3464.9	2.1, 8.0	
	# of BLQ/ALQ Values	0/0	4/0	
Week 3	N	5	7	0.0021
	MEAN, GEO MEAN	851.7, 735.9	2.1, 2.1	
	SD, SE	470.78, 210.54	0.00, 0.00	
	MEDIAN	944.7	2.1	
	MIN, MAX	320.1, 1481.4	2.1, 2.1	
	5%, 95%	320.1, 1481.4	2.1, 2.1	
	# of BLQ/ALQ Values	0/0	7/0	
Overall ^b	N	6	7	0.0021
	MEAN, GEO MEAN	1378.8, 1040.3	2.4, 2.3	
	SD, SE	1139.66, 465.26	0.76, 0.29	
	MEDIAN	879.4	2.1	
	MIN, MAX	445.2, 3222.8	2.1, 4.1	
	5%, 95%	445.2, 3222.8	2.1, 4.1	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438608

Final Draft: 22 October 2003

Page 639 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 245 of 264)

Biomarker: Total Nicotine ((nmol/L)/cigarette per day)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	701.4, 395.7		
	SD, SE	880.12, 359.31		
	MEDIAN	404.2		
	MIN, MAX	123.4, 2426.0		
	5%, 95%	123.4, 2426.0		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	778.0, 504.8		
	SD, SE	724.77, 295.89		
	MEDIAN	531.5		
	MIN, MAX	147.7, 1942.0		
	5%, 95%	147.7, 1942.0		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	528.0, 415.4		
	SD, SE	386.33, 172.77		
	MEDIAN	329.0		
	MIN, MAX	140.5, 1085.8		
	5%, 95%	140.5, 1085.8		
	# of BLQ/ALQ Values	0/0		
Overall*	N	6		NA
	MEAN, GEO MEAN	677.1, 490.8		
	SD, SE	573.72, 234.22		
	MEDIAN	562.7		
	MIN, MAX	137.2, 1709.7		
	5%, 95%	137.2, 1709.7		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234) will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438609

Final Draft: 22 October 2003

Page 640 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 246 of 264)

Biomarker: Total Nicotine ((ng/mL)/cigarette per day)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	113.8, 64.2		
	SD, SE	142.76, 58.28		
	MEDIAN	65.6		
	MIN, MAX	20.0, 393.5		
	5%, 95%	20.0, 393.5		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	126.2, 81.9		
	SD, SE	117.55, 47.99		
	MEDIAN	86.2		
	MIN, MAX	24.0, 315.0		
	5%, 95%	24.0, 315.0		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	85.7, 67.4		
	SD, SE	62.66, 28.02		
	MEDIAN	53.4		
	MIN, MAX	22.8, 176.1		
	5%, 95%	22.8, 176.1		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	6		NA
	MEAN, GEO MEAN	109.9, 79.7		
	SD, SE	93.03, 37.98		
	MEDIAN	91.3		
	MIN, MAX	22.3, 277.3		
	5%, 95%	22.3, 277.3		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438610

Final Draft: 22 October 2003

Page 641 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 247 of 264)

Biomarker: Trans-3-hydroxycotinine (nmol/24hr) Analytical Lab: INBIFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	8	0.0024
	MEAN, GEO MEAN	27286.763, 24423.243	27.743, 20.815	
	SD, SE	13018.2385, 5314.6736	19.8790, 7.0283	
	MEDIAN	26551.035	23.760	
	MIN, MAX	9903.928, 47408.910	5.880, 56.550	
	5%, 95%	9903.928, 47408.910	5.880, 56.550	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	6	7	0.0034
	MEAN, GEO MEAN	28780.750, 23570.930	26.811, 22.854	
	SD, SE	20864.6837, 8517.9715	15.6177, 5.9029	
	MEDIAN	24714.348	23.120	
	MIN, MAX	9062.489, 67799.170	10.712, 47.850	
	5%, 95%	9062.489, 67799.170	10.712, 47.850	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	5	5	0.0122
	MEAN, GEO MEAN	20684.366, 15880.862	22.055, 19.578	
	SD, SE	17932.5493, 8019.6799	11.5204, 5.1521	
	MEDIAN	13910.514	18.228	
	MIN, MAX	5533.662, 51582.300	9.450, 36.375	
	5%, 95%	5533.662, 51582.300	9.450, 36.375	
	# of BLQ/ALQ Values	0/0	0/0	
Overall ^b	N	6	8	0.0024
	MEAN, GEO MEAN	26279.497, 22293.290	23.547, 19.730	
	SD, SE	16487.3011, 6730.9125	13.4248, 4.7464	
	MEDIAN	21636.072	24.725	
	MIN, MAX	8166.693, 55596.793	8.681, 38.675	
	5%, 95%	8166.693, 55596.793	8.681, 38.675	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438611

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 248 of 264)

Biomarker: Trans-3-hydroxycotinine (µg/24hr)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	8	0.0024
	MEAN, GEO MEAN	5244.516, 4694.147	5.332, 4.000	
	SD, SE	2502.1057, 1021.4804	3.8207, 1.3508	
	MEDIAN	5103.109	4.567	
	MIN, MAX	1903.535, 9111.993	1.130, 10.869	
	5%, 95%	1903.535, 9111.993	1.130, 10.869	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	6	7	0.0034
	MEAN, GEO MEAN	5531.660, 4530.332	5.153, 4.393	
	SD, SE	4010.1922, 1637.1541	3.0018, 1.1346	
	MEDIAN	4750.098	4.444	
	MIN, MAX	1741.810, 13031.000	2.059, 9.197	
	5%, 95%	1741.810, 13031.000	2.059, 9.197	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	5	5	0.0122
	MEAN, GEO MEAN	3975.535, 3052.302	4.239, 3.763	
	SD, SE	3446.6359, 1541.3824	2.2143, 0.9903	
	MEDIAN	2673.601	3.503	
	MIN, MAX	1063.570, 9914.118	1.816, 6.991	
	5%, 95%	1063.570, 9914.118	1.816, 6.991	
	# of BLQ/ALQ Values	0/0	0/0	
Overall ^b	N	6	8	0.0024
	MEAN, GEO MEAN	5050.920, 4284.770	4.526, 3.792	
	SD, SE	3168.8595, 1293.6815	2.5804, 0.9123	
	MEDIAN	4158.453	4.752	
	MIN, MAX	1569.638, 10685.704	1.668, 7.433	
	5%, 95%	1569.638, 10685.704	1.668, 7.433	
	# of BLQ/ALQ Values	0/0	0/0	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438612

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 249 of 264)

Biomarker: Trans-3-hydroxycotinine ((nmol/24hr)/cigarette per day)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	1560.823, 1486.474		
	SD, SE	503.6919, 205.6314		
	MEDIAN	1524.586		
	MIN, MAX	786.539, 2370.446		
	5%, 95%	786.539, 2370.446		
Week 2	# of BLQ/ALQ Values	0/0		NA
	N	6		
	MEAN, GEO MEAN	2176.587, 1786.231		
	SD, SE	1569.9617, 640.9342		
	MEDIAN	1465.382		
	MIN, MAX	906.249, 4801.595		
Week 3	5%, 95%	906.249, 4801.595		NA
	# of BLQ/ALQ Values	0/0		
	N	5		
	MEAN, GEO MEAN	1617.681, 1453.841		
	SD, SE	790.0583, 353.3248		
	MEDIAN	1585.017		
Overall ^b	MIN, MAX	772.806, 2579.115		NA
	5%, 95%	772.806, 2579.115		
	# of BLQ/ALQ Values	0/0		
	N	6		
	MEAN, GEO MEAN	1781.061, 1665.949		
	SD, SE	729.6039, 297.8596		
Overall ^b	MEDIAN	1518.531		NA
	MIN, MAX	1103.963, 2779.840		
	5%, 95%	1103.963, 2779.840		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438613

Final Draft: 22 October 2003

Page 644 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 250 of 264)

Biomarker: Trans-3-hydroxycotinine ((µg/24hr)/cigarette per day)		Analytical Lab: INDIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	299.990, 285.700		
	SD, SE	96.8096, 39.5224		
	MEDIAN	293.026		
	MIN, MAX	151.173, 455.600		
	5%, 95%	151.173, 455.600		
Week 2	# of BLQ/ALQ Values	0/0		NA
	N	6		
	MEAN, GEO MEAN	418.340, 343.314		
	SD, SE	301.7467, 123.1876		
	MEDIAN	281.646		
	MIN, MAX	174.181, 922.867		
Week 3	5%, 95%	174.181, 922.867		NA
	# of BLQ/ALQ Values	0/0		
	N	5		
	MEAN, GEO MEAN	310.918, 279.428		
	SD, SE	151.8493, 67.9091		
	MEDIAN	304.640		
Overall ^b	MIN, MAX	148.533, 495.706		NA
	5%, 95%	148.533, 495.706		
	# of BLQ/ALQ Values	0/0		
	N	6		
	MEAN, GEO MEAN	342.320, 320.195		
	SD, SE	140.2297, 57.2485		
Overall ^b	MEDIAN	291.862		NA
	MIN, MAX	212.182, 534.285		
	5%, 95%	212.182, 534.285		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234^a will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438614

Final Draft: 22 October 2003

Page 645 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 251 of 264)

Biomarker: Trans-3-hydroxycotinine (nmol/mg Creatinine)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6	8	0.0024
	MEAN, GEO MEAN	21.591, 17.695	0.018, 0.014	
	SD, SE	17.3519, 7.0839	0.0129, 0.0046	
	MEDIAN	16.395	0.014	
	MIN, MAX	8.155, 55.986	0.005, 0.041	
	5%, 95%	8.155, 55.986	0.005, 0.041	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	6	7	0.0034
	MEAN, GEO MEAN	23.863, 18.574	0.016, 0.015	
	SD, SE	22.4716, 9.1740	0.0066, 0.0025	
	MEDIAN	15.847	0.017	
	MIN, MAX	9.465, 68.993	0.008, 0.024	
	5%, 95%	9.465, 68.993	0.008, 0.024	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	5	5	0.0119
	MEAN, GEO MEAN	19.402, 15.516	0.018, 0.015	
	SD, SE	17.0839, 7.6401	0.0108, 0.0048	
	MEDIAN	12.774	0.016	
	MIN, MAX	9.346, 49.656	0.008, 0.032	
	5%, 95%	9.346, 49.656	0.008, 0.032	
	# of BLQ/ALQ Values	0/0	0/0	
Overall ^b	N	6	8	0.0024
	MEAN, GEO MEAN	21.660, 17.595	0.016, 0.013	
	SD, SE	18.2969, 7.4697	0.0094, 0.0033	
	MEDIAN	15.202	0.014	
	MIN, MAX	9.166, 58.212	0.005, 0.032	
	5%, 95%	9.166, 58.212	0.005, 0.032	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438615

Final Draft: 22 October 2003

Page 646 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 252 of 264)

Biomarker: Trans-3-hydroxycotinine (µg/mg Creatinine)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6	8	0.0023
	MEAN, GEO MEAN	4.150, 3.401	0.003, 0.003	
	SD, SE	3.3353, 1.3616	0.0025, 0.0009	
	MEDIAN	3.151	0.003	
	MIN, MAX	1.567, 10.761	0.001, 0.008	
	5%, 95%	1.567, 10.761	0.001, 0.008	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	6	7	0.0032
	MEAN, GEO MEAN	4.586, 3.570	0.003, 0.003	
	SD, SE	4.3189, 1.7632	0.0012, 0.0005	
	MEDIAN	3.046	0.003	
	MIN, MAX	1.819, 13.260	0.002, 0.005	
	5%, 95%	1.819, 13.260	0.002, 0.005	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	5	5	0.0119
	MEAN, GEO MEAN	3.729, 2.982	0.004, 0.003	
	SD, SE	3.2837, 1.4685	0.0018, 0.0008	
	MEDIAN	2.455	0.003	
	MIN, MAX	1.796, 9.544	0.002, 0.006	
	5%, 95%	1.796, 9.544	0.002, 0.006	
	# of BLQ/ALQ Values	0/0	0/0	
Overall*	N	6	8	0.0024
	MEAN, GEO MEAN	4.163, 3.382	0.003, 0.003	
	SD, SE	3.5166, 1.4356	0.0016, 0.0006	
	MEDIAN	2.922	0.003	
	MIN, MAX	1.761, 11.188	0.001, 0.006	
	5%, 95%	1.761, 11.188	0.001, 0.006	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438616

Final Draft: 22 October 2003

Page 647 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 253 of 264)

Biomarker: Trans-3-hydroxycotinine ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	1.241, 1.077		
	SD, SE	0.8099, 0.3306		
	MEDIAN	0.966		
	MIN, MAX	0.560, 2.799		
	5%, 95%	0.560, 2.799		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	1.719, 1.408		
	SD, SE	1.2049, 0.4919		
	MEDIAN	1.126		
	MIN, MAX	0.623, 3.450		
	5%, 95%	0.623, 3.450		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	1.611, 1.420		
	SD, SE	0.7635, 0.3415		
	MEDIAN	1.646		
	MIN, MAX	0.519, 2.483		
	5%, 95%	0.519, 2.483		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	6		NA
	MEAN, GEO MEAN	1.486, 1.321		
	SD, SE	0.8156, 0.3330		
	MEDIAN	1.255		
	MIN, MAX	0.645, 2.911		
	5%, 95%	0.645, 2.911		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438617

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 254 of 264)

Biomarker: Trans-3-hydroxycotinine ((µg/mg Creatinine)/cigarette per day) Analytical Lab: INBIFO

Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6		NA
	MEAN, GEO MEAN	0.239, 0.207		
	SD, SE	0.1555, 0.0635		
	MEDIAN	0.186		
	MIN, MAX	0.108, 0.538		
	5%, 95%	0.108, 0.538		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	0.330, 0.271		
	SD, SE	0.2315, 0.0945		
	MEDIAN	0.217		
	MIN, MAX	0.120, 0.663		
	5%, 95%	0.120, 0.663		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	0.310, 0.273		
	SD, SE	0.1466, 0.0655		
	MEDIAN	0.316		
	MIN, MAX	0.100, 0.477		
	5%, 95%	0.100, 0.477		
	# of BLQ/ALQ Values	0/0		
Overall*	N	6		NA
	MEAN, GEO MEAN	0.286, 0.254		
	SD, SE	0.1565, 0.0639		
	MEDIAN	0.241		
	MIN, MAX	0.124, 0.559		
	5%, 95%	0.124, 0.559		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438618

Final Draft: 22 October 2003

Page 649 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 255 of 264)

Biomarker: Trans-3-hydroxycotinine (nmol/L)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	8	0.0024
	MEAN, GEO MEAN	15531.5, 14510.3	12.9, 10.0	
	SD, SE	5703.03, 2328.25	9.94, 3.51	
	MEDIAN	16253.2	8.3	
	MIN, MAX	7282.3, 21708.6	4.9, 31.9	
	5%, 95%	7282.3, 21708.6	4.9, 31.9	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	6	7	0.0034
	MEAN, GEO MEAN	16215.6, 13989.4	12.7, 10.9	
	SD, SE	8993.85, 3671.72	7.86, 2.97	
	MEDIAN	14730.5	10.3	
	MIN, MAX	5006.9, 30541.0	6.0, 27.6	
	5%, 95%	5006.9, 30541.0	6.0, 27.6	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	5	5	0.0122
	MEAN, GEO MEAN	10483.2, 8939.9	11.3, 10.7	
	SD, SE	6664.13, 2980.29	4.09, 1.83	
	MEDIAN	8860.2	12.4	
	MIN, MAX	4009.9, 21054.0	7.0, 16.9	
	5%, 95%	4009.9, 21054.0	7.0, 16.9	
	# of BLQ/ALQ Values	0/0	0/0	
Overall ^b	N	6	8	0.0024
	MEAN, GEO MEAN	14945.7, 13284.5	11.3, 10.0	
	SD, SE	7410.05, 3025.14	6.05, 2.14	
	MEDIAN	14143.7	10.6	
	MIN, MAX	5433.0, 26124.8	5.5, 22.2	
	5%, 95%	5433.0, 26124.8	5.5, 22.2	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438619

Final Draft: 22 October 2003

Page 650 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 256 of 264)

Biomarker: Trans-3-hydroxycotinine (ng/mL)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6	8	0.0024
	MEAN, GEO MEAN	2985.2, 2788.9	2.5, 1.9	
	SD, SE	1096.11, 447.48	1.92, 0.68	
	MEDIAN	3123.9	1.6	
	MIN, MAX	1399.7, 4172.4	0.9, 6.1	
	5%, 95%	1399.7, 4172.4	0.9, 6.1	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	6	7	0.0034
	MEAN, GEO MEAN	3116.6, 2688.7	2.4, 2.1	
	SD, SE	1728.63, 705.71	1.50, 0.57	
	MEDIAN	2831.2	2.0	
	MIN, MAX	962.3, 5870.0	1.2, 5.3	
	5%, 95%	962.3, 5870.0	1.2, 5.3	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	5	5	0.0119
	MEAN, GEO MEAN	2014.9, 1718.2	2.1, 2.0	
	SD, SE	1280.85, 572.81	0.79, 0.35	
	MEDIAN	1702.9	2.4	
	MIN, MAX	770.7, 4046.6	1.3, 3.2	
	5%, 95%	770.7, 4046.6	1.3, 3.2	
	# of BLQ/ALQ Values	0/0	0/0	
Overall*	N	6	8	0.0024
	MEAN, GEO MEAN	2872.6, 2553.3	2.2, 1.9	
	SD, SE	1424.22, 581.44	1.15, 0.40	
	MEDIAN	2718.4	2.0	
	MIN, MAX	1044.2, 5021.2	1.1, 4.2	
	5%, 95%	1044.2, 5021.2	1.1, 4.2	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234) will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438620

Final Draft: 22 October 2003

Page 651 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 257 of 264)

Biomarker: Trans-3-hydroxycotinine ((nmol/L)/cigarette per day)		Analytical Lab: INBIFO		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6		NA
	MEAN, GEO MEAN	992.0, 883.1		
	SD, SE	474.97, 193.91		
	MEDIAN	920.8		
	MIN, MAX	321.0, 1758.1		
	5%, 95%	321.0, 1758.1		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	1222.6, 1060.1		
	SD, SE	663.49, 270.87		
	MEDIAN	1276.8		
	MIN, MAX	500.7, 2233.3		
	5%, 95%	500.7, 2233.3		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	854.5, 818.4		
	SD, SE	258.22, 115.48		
	MEDIAN	1022.6		
	MIN, MAX	492.2, 1052.7		
	5%, 95%	492.2, 1052.7		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	6		NA
	MEAN, GEO MEAN	1044.2, 1007.3		
	SD, SE	292.56, 119.44		
	MEDIAN	1092.5		
	MIN, MAX	636.9, 1413.6		
	5%, 95%	636.9, 1413.6		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438621

Final Draft: 22 October 2003

Page 652 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 258 of 264)

Biomarker: Trans-3-hydroxycotinine ((ng/mL)/cigarette per day)		Analytical Lab: INBIFO	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	6	
	MEAN, GEO MEAN	190.7, 169.7	
	SD, SE	91.29, 37.27	
	MEDIAN	177.0	
	MIN, MAX	61.7, 337.9	
	5%, 95%	61.7, 337.9	
	# of BLQ/ALQ Values	0/0	
Week 2	N	6	
	MEAN, GEO MEAN	235.0, 203.8	
	SD, SE	127.51, 52.06	
	MEDIAN	245.4	
	MIN, MAX	96.2, 429.2	
	5%, 95%	96.2, 429.2	
	# of BLQ/ALQ Values	0/0	
Week 3	N	5	
	MEAN, GEO MEAN	164.2, 157.3	
	SD, SE	49.61, 22.19	
	MEDIAN	196.5	
	MIN, MAX	94.6, 202.3	
	5%, 95%	94.6, 202.3	
	# of BLQ/ALQ Values	0/0	
Overall*	N	6	
	MEAN, GEO MEAN	200.7, 193.6	
	SD, SE	56.23, 22.96	
	MEDIAN	210.0	
	MIN, MAX	122.4, 271.7	
	5%, 95%	122.4, 271.7	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438622

Final Draft: 22 October 2003

Page 653 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 259 of 264)

Biomarker: Trans-3-hydroxycotinine-O-glucuronide (nmol/L)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	2	0.0668
	MEAN, GEO MEAN	3229.3, 2944.6	18.1, 17.2	
	SD, SE	1244.01, 507.87	7.71, 5.45	
	MEDIAN	3884.0	18.1	
	MIN, MAX	1134.7, 4122.8	12.6, 23.5	
	5%, 95%	1134.7, 4122.8	12.6, 23.5	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	6	1	NA
	MEAN, GEO MEAN	3761.5, 3336.9	14.3, 14.3	
	SD, SE	2090.68, 853.52	NA, NA	
	MEDIAN	2948.4	14.3	
	MIN, MAX	1937.9, 7148.3	14.3, 14.3	
	5%, 95%	1937.9, 7148.3	NA, NA	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	5		NA
	MEAN, GEO MEAN	2442.3, 1338.9		
	SD, SE	2744.27, 1227.28		
	MEDIAN	1240.5		
	MIN, MAX	270.0, 6900.4		
	5%, 95%	270.0, 6900.4		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	6	2	0.0668
	MEAN, GEO MEAN	3314.7, 2908.5	18.5, 17.8	
	SD, SE	1730.35, 706.41	7.07, 5.00	
	MEDIAN	3199.8	18.5	
	MIN, MAX	1319.5, 5509.1	13.5, 23.5	
	5%, 95%	1319.5, 5509.1	13.5, 23.5	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438623

Final Draft: 22 October 2003

Page 654 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 260 of 264)

Biomarker: Trans-3-hydroxycotinine-O-glucuronide (nmol/L/cigarette per day)		Analytical Lab: INBIFO	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	6	
	MEAN, GEO MEAN	197.4, 179.2	
	SD, SE	83.47, 34.08	
	MEDIAN	196.9	
	MIN, MAX	68.4, 324.8	
	5%, 95%	68.4, 324.8	
	# of BLQ/ALQ Values	0/0	
Week 2	N	6	
	MEAN, GEO MEAN	288.2, 252.9	
	SD, SE	144.58, 59.02	
	MEDIAN	306.4	
	MIN, MAX	96.9, 494.5	
	5%, 95%	96.9, 494.5	
	# of BLQ/ALQ Values	0/0	
Week 3	N	5	
	MEAN, GEO MEAN	179.5, 122.6	
	SD, SE	137.74, 61.60	
	MEDIAN	206.8	
	MIN, MAX	32.1, 345.0	
	5%, 95%	32.1, 345.0	
	# of BLQ/ALQ Values	0/0	
Overall ^b	N	6	
	MEAN, GEO MEAN	226.3, 213.1	
	SD, SE	84.55, 34.52	
	MEDIAN	225.0	
	MIN, MAX	119.3, 362.6	
	5%, 95%	119.3, 362.6	

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438624

Final Draft: 22 October 2003

Page 655 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 261 of 264)

Biomarker: Trans-3-hydroxycotinine-O-glucuronide (nmol/24hr)		Analytical Lab: INBIFO		P-value*
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	6	2	0.0668
	MEAN, GEO MEAN	5915.230, 4956.210	46.567, 35.776	
	SD, SE	3528.2682, 1440.4094	42.1556, 29.8085	
	MEDIAN	5879.115	46.567	
	MIN, MAX	1543.192, 11872.310	16.758, 76.375	
	5%, 95%	1543.192, 11872.310	16.758, 76.375	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	6	1	NA
	MEAN, GEO MEAN	5976.365, 5622.441	24.024, 24.024	
	SD, SE	2460.4198, 1004.4622	NA, NA	
	MEDIAN	4840.694	24.024	
	MIN, MAX	3837.042, 10362.680	24.024, 24.024	
	5%, 95%	3837.042, 10362.680	NA, NA	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	5		NA
	MEAN, GEO MEAN	5169.565, 2378.384		
	SD, SE	6804.7412, 3043.1728		
	MEDIAN	2667.075		
	MIN, MAX	372.600, 16905.980		
	5%, 95%	372.600, 16905.980		
	# of BLQ/ALQ Values	0/0		
Overall*	N	6	2	0.0668
	MEAN, GEO MEAN	5777.447, 4931.665	48.383, 39.463	
	SD, SE	3856.0276, 1574.2167	39.5867, 27.9920	
	MEDIAN	4375.768	48.383	
	MIN, MAX	2179.450, 13046.990	20.391, 76.375	
	5%, 95%	2179.450, 13046.990	20.391, 76.375	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438625

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 262 of 264)

Biomarker: Trans-3-hydroxycotinine-O-glucuronide (nmol/24hr/cigarette per day)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	6		NA
	MEAN, GEO MEAN	326.104, 301.650		
	SD, SE	148.2217, 60.5112		
	MEDIAN	276.753		
	MIN, MAX	167.506, 593.616		
	5%, 95%	167.506, 593.616		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	461.555, 426.075		
	SD, SE	189.3290, 77.2932		
	MEDIAN	461.075		
	MIN, MAX	191.852, 769.055		
	5%, 95%	191.852, 769.055		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	363.714, 217.734		
	SD, SE	328.0110, 146.6910		
	MEDIAN	416.278		
	MIN, MAX	50.380, 845.299		
	5%, 95%	50.380, 845.299		
	# of BLQ/ALQ Values	0/0		
Overall*	N	6		NA
	MEAN, GEO MEAN	381.335, 355.488		
	SD, SE	159.8954, 65.2770		
	MEDIAN	352.888		
	MIN, MAX	209.009, 652.350		
	5%, 95%	209.009, 652.350		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438626

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 263 of 264)

Biomarker: Trans-3-hydroxycotinine-O-glucuronide (nmol/mg Creatinine) Analytical Lab: INBIFO				
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6	2	0.0668
	MEAN, GEO MEAN	4.796, 3.591	0.031, 0.020	
	SD, SE	4.6266, 1.8888	0.0339, 0.0240	
	MEDIAN	3.582	0.031	
	MIN, MAX	1.271, 14.020	0.007, 0.055	
	5%, 95%	1.271, 14.020	0.007, 0.055	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	6	1	NA
	MEAN, GEO MEAN	4.998, 4.431	0.009, 0.009	
	SD, SE	2.9163, 1.1906	NA, NA	
	MEDIAN	4.687	0.009	
	MIN, MAX	2.318, 10.545	0.009, 0.009	
	5%, 95%	2.318, 10.545	NA, NA	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	5		NA
	MEAN, GEO MEAN	4.826, 2.324		
	SD, SE	6.5574, 2.9326		
	MEDIAN	2.547		
	MIN, MAX	0.609, 16.275		
	5%, 95%	0.609, 16.275		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	6	2	0.0668
	MEAN, GEO MEAN	4.837, 3.842	0.032, 0.021	
	SD, SE	4.3685, 1.7834	0.0332, 0.0235	
	MEDIAN	3.397	0.032	
	MIN, MAX	2.192, 13.613	0.008, 0.055	
	5%, 95%	2.192, 13.613	0.008, 0.055	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438627

Final Draft: 22 October 2003

Page 658 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-2
Statistical Comparison Between Smokers and Non-Smokers of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 264 of 264)

Biomarker: Trans-3-hydroxycotinine-O-glucuronide ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: INBIFO		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	6		NA
	MEAN, GEO MEAN	0.265, 0.219		
	SD, SE	0.2168, 0.0885		
	MEDIAN	0.201		
	MIN, MAX	0.119, 0.701		
	5%, 95%	0.119, 0.701		
	# of BLQ/ALQ Values	0/0		
Week 2	N	6		NA
	MEAN, GEO MEAN	0.378, 0.336		
	SD, SE	0.1636, 0.0668		
	MEDIAN	0.449		
	MIN, MAX	0.116, 0.527		
	5%, 95%	0.116, 0.527		
	# of BLQ/ALQ Values	0/0		
Week 3	N	5		NA
	MEAN, GEO MEAN	0.344, 0.213		
	SD, SE	0.3074, 0.1375		
	MEDIAN	0.336		
	MIN, MAX	0.034, 0.814		
	5%, 95%	0.034, 0.814		
	# of BLQ/ALQ Values	0/0		
Overall ^b	N	6		NA
	MEAN, GEO MEAN	0.321, 0.278		
	SD, SE	0.1946, 0.0795		
	MEDIAN	0.293		
	MIN, MAX	0.118, 0.681		
	5%, 95%	0.118, 0.681		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., "<1.234" will be used as "1.234") for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438628

Final Draft: 22 October 2003

Page 659 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-3
Statistical Comparison Between Smokers and Non-Smokers of Exhale Biomarkers of Exposure by Timepoint and Overall
(Page 1 of 8)

Biomarker: Acetonitrile (nL/L @20 °C and 1 atm)		Analytical Lab: Madison		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	50	65	0.0020
	MEAN, GEO MEAN	12771.286, 2830.905	23024.374, 9604.280	
	SD, SE	16174.6257, 2287.4375	20647.3178, 2560.9846	
	MEDIAN	7559.747	19298.217	
	MIN, MAX	27.047, 61266.718	27.047, 90418.051	
	5%, 95%	27.047, 43336.359	92.902, 54497.370	
	# of BLQ/ALQ Values	3/12	2/0	
Week 3	N	46	65	0.0003
	MEAN, GEO MEAN	14740.147, 4167.738	25525.906, 16294.636	
	SD, SE	15322.4372, 2259.1701	15334.1170, 1901.9631	
	MEDIAN	11061.267	25973.434	
	MIN, MAX	27.047, 55212.198	27.047, 64440.436	
	5%, 95%	360.626, 41797.811	571.554, 48358.890	
	# of BLQ/ALQ Values	1/14	1/0	
Week 6	N	42	65	<.0001
	MEAN, GEO MEAN	13484.527, 3570.907	25638.963, 17780.694	
	SD, SE	15300.2649, 2360.8821	13884.4733, 1722.1570	
	MEDIAN	6200.319	28505.088	
	MIN, MAX	27.047, 57117.622	143.534, 58955.534	
	5%, 95%	360.626, 38261.231	2225.726, 46880.251	
	# of BLQ/ALQ Values	2/12	0/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	14217.256, 5394.281	24729.748, 21455.756	
	SD, SE	13608.7604, 1924.5694	11459.6009, 1421.3886	
	MEDIAN	13301.411	24283.147	
	MIN, MAX	138.408, 61266.718	2561.353, 52452.649	
	5%, 95%	249.433, 41598.061	6272.987, 39744.215	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438629

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-3
Statistical Comparison Between Smokers and Non-Smokers of Exhale Biomarkers of Exposure by Timepoint and Overall
(Page 2 of 8)

Biomarker: Acetonitrile (nmol/L)		Analytical Lab: Madison		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	50	65	0.0020
	MEAN, GEO MEAN	530.898, 117.677	957.116, 399.243	
	SD, SE	672.3739, 95.0880	858.3023, 106.4593	
	MEDIAN	314.257	802.221	
	MIN, MAX	1.124, 2546.837	1.124, 3758.649	
	5%, 95%	1.124, 1801.478	3.862, 2265.438	
	# of BLQ/ALQ Values	3/12	2/0	
Week 3	N	46	65	0.0003
	MEAN, GEO MEAN	612.743, 173.250	1061.103, 677.359	
	SD, SE	636.9487, 93.9130	637.4342, 79.0640	
	MEDIAN	459.814	1079.707	
	MIN, MAX	1.124, 2295.153	1.124, 2678.768	
	5%, 95%	14.991, 1737.521	23.759, 2010.263	
	# of BLQ/ALQ Values	1/14	1/0	
Week 6	N	42	65	<.0001
	MEAN, GEO MEAN	560.547, 148.439	1065.803, 739.139	
	SD, SE	636.0270, 98.1411	577.1730, 71.5895	
	MEDIAN	257.745	1184.947	
	MIN, MAX	1.124, 2374.361	5.968, 2450.762	
	5%, 95%	14.991, 1590.507	92.523, 1948.797	
	# of BLQ/ALQ Values	2/12	0/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	591.007, 224.238	1028.007, 891.909	
	SD, SE	565.7117, 80.0037	476.3719, 59.0867	
	MEDIAN	552.935	1009.442	
	MIN, MAX	5.753, 2546.837	106.475, 2180.439	
	5%, 95%	10.369, 1729.218	260.766, 1652.154	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438630

Final Draft: 22 October 2003

Page 661 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-3
Statistical Comparison Between Smokers and Non-Smokers of Exhale Biomarkers of Exposure by Timepoint and Overall
(Page 3 of 8)

Biomarker: Acetonitrile ((nL/L @20 °C and 1 atm)/cigarette per day)		Analytical Lab: Madison	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	1086.236, 217.463	
	SD, SE	2682.8000, 379.4052	
	MEDIAN	546.023	
	MIN, MAX	1.378, 18842.877	
	5%, 95%	2.254, 2802.105	
	# of BLQ/ALQ Values	3/12	
Week 3	N	46	
	MEAN, GEO MEAN	1430.704, 332.223	
	SD, SE	2317.4116, 341.6837	
	MEDIAN	833.470	
	MIN, MAX	1.803, 13126.227	
	5%, 95%	18.031, 5639.894	
	# of BLQ/ALQ Values	1/14	
Week 6	N	42	
	MEAN, GEO MEAN	1495.642, 267.395	
	SD, SE	3294.4494, 508.3446	
	MEDIAN	378.483	
	MIN, MAX	1.352, 19039.207	
	5%, 95%	14.425, 5729.977	
	# of BLQ/ALQ Values	2/12	
Overall*	N	50	
	MEAN, GEO MEAN	1355.640, 435.265	
	SD, SE	1920.0254, 271.5326	
	MEDIAN	877.738	
	MIN, MAX	6.920, 11017.118	
	5%, 95%	15.627, 4456.056	
			NA

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438631

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-3
Statistical Comparison Between Smokers and Non-Smokers of Exhale Biomarkers of Exposure by Timepoint and Overall
(Page 4 of 8)

Biomarker: Acetonitrile ((nmol/L)/cigarette per day)		Analytical Lab: Madison		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	45.154, 9.039		
	SD, SE	111.5231, 15.7717		
	MEDIAN	22.698		
	MIN, MAX	0.057, 783.292		
	5%, 95%	0.094, 116.483		
	# of BLQ/ALQ Values	3/12		
Week 3	N	46		NA
	MEAN, GEO MEAN	59.474, 13.812		
	SD, SE	96.3340, 14.2037		
	MEDIAN	34.647		
	MIN, MAX	0.075, 545.633		
	5%, 95%	0.750, 234.449		
	# of BLQ/ALQ Values	1/14		
Week 6	N	42		NA
	MEAN, GEO MEAN	62.173, 11.116		
	SD, SE	136.9492, 21.1317		
	MEDIAN	15.734		
	MIN, MAX	0.056, 791.454		
	5%, 95%	0.600, 238.193		
	# of BLQ/ALQ Values	2/12		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	56.354, 18.095		
	SD, SE	79.8149, 11.2875		
	MEDIAN	36.487		
	MIN, MAX	0.288, 457.978		
	5%, 95%	0.650, 185.237		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438632

Final Draft: 22 October 2003

Page 663 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-3
Statistical Comparison Between Smokers and Non-Smokers of Exhaled Biomarkers of Exposure by Timepoint and Overall
(Page 5 of 8)

Biomarker: Acetonitrile (ng/mL)		Analytical Lab: Madison		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*
Week 1	N	50	65	0.0020
	MEAN, GEO MEAN	3541422.49, 784997.78	6384559.49, 2663225.25	
	SD, SE	4485153.910, 634296.549	5725412.124, 710149.973	
	MEDIAN	2096285.14	5351312.21	
	MIN, MAX	7500.00, 16988996.62	7500.00, 25072535.47	
	5%, 95%	7500.00, 12016985.39	25761.32, 15111885.45	
	# of BLQ/ALQ Values	3/12	2/0	
Week 3	N	46	65	0.0003
	MEAN, GEO MEAN	4087379.02, 1155695.46	7078223.49, 4518431.88	
	SD, SE	4248845.728, 626458.126	4252084.490, 527406.171	
	MEDIAN	3067241.42	7202321.10	
	MIN, MAX	7500.00, 15310104.26	7500.00, 17869054.85	
	5%, 95%	100000.00, 11590352.68	158489.34, 13409711.46	
	# of BLQ/ALQ Values	1/14	1/0	
Week 6	N	42	65	<.0001
	MEAN, GEO MEAN	3739201.06, 990195.87	7109573.85, 4930509.83	
	SD, SE	4242697.448, 654662.429	3850104.529, 477546.693	
	MEDIAN	1719321.63	7904337.84	
	MIN, MAX	7500.00, 15838470.03	39806.96, 16348115.24	
	5%, 95%	100000.00, 10609674.23	617184.22, 12999691.34	
	# of BLQ/ALQ Values	2/12	0/0	
Overall*	N	50	65	<.0001
	MEAN, GEO MEAN	3942383.60, 1495810.65	6857452.28, 5949588.46	
	SD, SE	3773650.566, 533674.781	3177697.892, 394144.915	
	MEDIAN	3688423.85	6733611.88	
	MIN, MAX	38379.95, 16988996.62	710251.93, 14544893.17	
	5%, 95%	69166.67, 11534962.73	1739472.33, 11020899.43	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234) will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438633

Final Draft: 22 October 2003

Page 664 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-3
Statistical Comparison Between Smokers and Non-Smokers of Exhale Biomarkers of Exposure by Timepoint and Overall
(Page 6 of 8)

Biomarker: Acetonitrile ((ng/mL)/cigarette per day)		Analytical Lab: Madison		P-value ^a
Timepoint	Statistic	Smokers	Non-Smokers	
Week 1	N	50		NA
	MEAN, GEO MEAN	301208.44, 60301.04		
	SD, SE	743928.886, 105207.432		
	MEDIAN	151409.90		
	MIN, MAX	381.99, 5225048.61		
	5%, 95%	625.00, 777011.51		
	# of BLQ/ALQ Values	3/12		
Week 3	N	46		NA
	MEAN, GEO MEAN	396728.13, 92124.35		
	SD, SE	642608.244, 94747.417		
	MEDIAN	231117.50		
	MIN, MAX	500.00, 3639846.15		
	5%, 95%	5000.00, 1563918.26		
	# of BLQ/ALQ Values	1/14		
Week 6	N	42		NA
	MEAN, GEO MEAN	414735.01, 74148.18		
	SD, SE	913536.611, 140961.759		
	MEDIAN	104951.71		
	MIN, MAX	375.00, 5279490.01		
	5%, 95%	4000.00, 1588897.93		
	# of BLQ/ALQ Values	2/12		
Overall ^b	N	50		NA
	MEAN, GEO MEAN	375913.22, 120697.61		
	SD, SE	532414.763, 75294.818		
	MEDIAN	243392.79		
	MIN, MAX	1919.00, 3054999.42		
	5%, 95%	4333.33, 1235645.07		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438634

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-3
Statistical Comparison Between Smokers and Non-Smokers of Exhale Biomarkers of Exposure by Timepoint and Overall
(Page 7 of 8)

Biomarker: Carbon monoxide (ppm)		Analytical Lab: CRF		
Timepoint	Statistic	Smokers	Non-Smokers	P-value ^a
Week 1	N	50	65	<.0001
	MEAN, GEO MEAN	26.3, 22.5	5.7, 5.5	
	SD, SE	14.89, 2.11	1.35, 0.17	
	MEDIAN	23.5	5.7	
	MIN, MAX	7.8, 71.4	3.6, 9.6	
	5%, 95%	8.6, 54.7	3.7, 8.1	
	# of BLQ/ALQ Values	0/0	0/0	
Week 2	N	49	65	<.0001
	MEAN, GEO MEAN	24.5, 20.3	5.1, 4.7	
	SD, SE	15.54, 2.22	1.60, 0.20	
	MEDIAN	21.2	5.2	
	MIN, MAX	4.5, 88.9	0.1, 9.6	
	5%, 95%	6.7, 50.1	3.2, 7.7	
	# of BLQ/ALQ Values	0/0	0/0	
Week 3	N	46	65	<.0001
	MEAN, GEO MEAN	26.3, 22.3	5.2, 4.9	
	SD, SE	14.50, 2.14	1.65, 0.20	
	MEDIAN	23.7	5.2	
	MIN, MAX	5.3, 62.2	0.3, 10.6	
	5%, 95%	7.2, 55.1	3.2, 8.3	
	# of BLQ/ALQ Values	0/0	0/0	
Week 6	N	42	65	<.0001
	MEAN, GEO MEAN	29.2, 25.0	6.2, 5.6	
	SD, SE	14.61, 2.25	2.44, 0.30	
	MEDIAN	27.0	5.8	
	MIN, MAX	4.0, 70.5	0.4, 13.8	
	5%, 95%	10.0, 51.1	3.6, 11.6	
	# of BLQ/ALQ Values	0/0	0/0	
Overall ^b	N	50	65	<.0001
	MEAN, GEO MEAN	26.2, 22.5	5.6, 5.5	
	SD, SE	14.18, 2.00	1.17, 0.15	
	MEDIAN	22.1	5.3	
	MIN, MAX	5.9, 66.0	3.1, 8.6	
	5%, 95%	9.5, 49.2	3.7, 7.8	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438635

Final Draft: 22 October 2003

Page 666 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.1-3
Statistical Comparison Between Smokers and Non-Smokers of Exhale Biomarkers of Exposure by Timepoint and Overall
(Page 8 of 8)

Biomarker: Carbon monoxide ((ppm)/cigarette per day)		Analytical Lab: CRF	
Timepoint	Statistic	Smokers	Non-Smokers
Week 1	N	50	
	MEAN, GEO MEAN	2.2, 1.7	
	SD, SE	2.26, 0.32	
	MEDIAN	1.6	
	MIN, MAX	0.5, 14.3	
	5%, 95%	0.6, 5.0	
	# of BLQ/ALQ Values	0/0	
Week 2	N	49	
	MEAN, GEO MEAN	2.3, 1.6	
	SD, SE	3.16, 0.45	
	MEDIAN	1.5	
	MIN, MAX	0.5, 22.1	
	5%, 95%	0.7, 4.9	
	# of BLQ/ALQ Values	0/0	
Week 3	N	46	
	MEAN, GEO MEAN	2.1, 1.8	
	SD, SE	1.66, 0.25	
	MEDIAN	1.7	
	MIN, MAX	0.6, 11.0	
	5%, 95%	0.8, 5.2	
	# of BLQ/ALQ Values	0/0	
Week 6	N	42	
	MEAN, GEO MEAN	2.8, 1.9	
	SD, SE	5.31, 0.82	
	MEDIAN	1.8	
	MIN, MAX	0.6, 35.3	
	5%, 95%	0.9, 6.8	
	# of BLQ/ALQ Values	0/0	
Overall*	N	50	
	MEAN, GEO MEAN	2.3, 1.8	
	SD, SE	2.83, 0.40	
	MEDIAN	1.8	
	MIN, MAX	0.6, 20.7	
	5%, 95%	0.8, 5.1	
			NA

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438636

Final Draft: 22 October 2003

Page 667 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

TABLE 14.2.1-4
Statistical Comparison Between AM and PM for Smokers and Non-Smokers of Selected Biomarkers of Exposure by Timepoint and Overall
(Page 1 of 9)

Biomarker: Carboxyhemoglobin (% saturation) Analytical Lab: CCLS

Gender	Timepoint	Statistic	Smokers			Non-Smokers		
			AM	PM	P-value*	AM	PM	P-value*
Female	Week 1	N	24	8	0.7938	23	12	0.5293
		MEAN, GEO MEAN	4.3, 3.3	4.9, 3.4		0.3, 0.3	0.3, 0.3	
		SD, SE	2.85, 0.58	3.84, 1.36		0.09, 0.02	0.06, 0.02	
		MEDIAN	3.2	4.5		0.3	0.3	
		MIN, MAX	0.8, 11.3	0.9, 11.4		0.3, 0.7	0.3, 0.5	
		5%, 95%	0.9, 8.9	0.9, 11.4		0.3, 0.4	0.3, 0.5	
		# of BLQ/ALQ Values	0/0	0/0		18/0	9/0	
	Week 2	N	22	9	0.3838	27	8	0.8869
		MEAN, GEO MEAN	4.4, 3.1	3.5, 2.2		0.3, 0.3	0.3, 0.3	
		SD, SE	3.33, 0.71	2.99, 1.00		0.05, 0.01	0.07, 0.03	
		MEDIAN	4.7	2.6		0.3	0.3	
		MIN, MAX	0.3, 13.3	0.3, 9.8		0.3, 0.5	0.3, 0.5	
		5%, 95%	0.6, 10.1	0.3, 9.8		0.3, 0.4	0.3, 0.5	
		# of BLQ/ALQ Values	1/0	1/0		23/0	7/0	
	Week 3	N	24	5	0.2143	28	7	0.0468
		MEAN, GEO MEAN	5.0, 4.1	3.7, 2.7		0.4, 0.4	0.7, 0.5	
		SD, SE	2.70, 0.55	3.19, 1.43		0.43, 0.08	0.81, 0.31	
		MEDIAN	4.3	3.1		0.3	0.4	
		MIN, MAX	0.3, 9.7	0.7, 9.1		0.3, 2.2	0.3, 2.5	
		5%, 95%	1.3, 9.3	0.7, 9.1		0.3, 1.6	0.3, 2.5	
		# of BLQ/ALQ Values	0/0	0/0		20/0	2/0	
	Week 6	N	22	6	0.6340	30	5	0.0544
		MEAN, GEO MEAN	4.7, 3.9	4.3, 2.4		0.4, 0.3	0.5, 0.4	
		SD, SE	2.41, 0.51	3.91, 1.60		0.21, 0.04	0.18, 0.08	
		MEDIAN	4.7	3.4		0.3	0.4	
		MIN, MAX	0.4, 9.8	0.3, 9.2		0.3, 1.3	0.3, 0.7	
		5%, 95%	1.0, 8.2	0.3, 9.2		0.3, 0.8	0.3, 0.7	
		# of BLQ/ALQ Values	0/0	1/0		21/0	1/0	

NOTE: AM refers to biomarker collection before noon, PM refers to biomarker collection at noon or after.

* P-value from Wilcoxon rank-sum test.

PM3006438637

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

TABLE 14.2.1-4
Statistical Comparison Between AM and PM for Smokers and Non-Smokers of Selected Biomarkers of Exposure by Timepoint and Overall
(Page 2 of 9)

Biomarker: Carboxyhemoglobin (% saturation) Analytical Lab: CCLS

Gender	Timepoint	Statistic	Smokers			Non-Smokers		
			AM	PM	P-value*	AM	PM	P-value*
Male	Week 1	N	10	8	0.7895	20	10	0.7820
		MEAN, GEO MEAN	4.9, 3.4	3.7, 3.1		0.5, 0.4	0.5, 0.4	
		SD, SE	4.10, 1.30	2.16, 0.76		0.21, 0.05	0.20, 0.06	
		MEDIAN	4.1	3.5		0.4	0.4	
		MIN, MAX	0.3, 14.8	0.9, 7.9		0.3, 1.0	0.3, 0.8	
		5%, 95%	0.3, 14.8	0.9, 7.9		0.3, 0.9	0.3, 0.8	
		# of BLQ/ALQ Values	1/0	0/0		7/0	3/0	
	Week 2	N	12	6	0.8883	24	6	0.7107
		MEAN, GEO MEAN	3.7, 2.6	3.8, 3.0		0.4, 0.4	0.5, 0.4	
		SD, SE	2.77, 0.80	2.79, 1.14		0.18, 0.04	0.35, 0.14	
		MEDIAN	3.0	3.5		0.3	0.3	
		MIN, MAX	0.3, 8.6	1.0, 8.4		0.3, 0.9	0.3, 1.1	
		5%, 95%	0.3, 8.6	1.0, 8.4		0.3, 0.8	0.3, 1.1	
		# of BLQ/ALQ Values	1/0	0/0		14/0	3/0	
	Week 3	N	13	4	0.8207	23	7	0.8679
		MEAN, GEO MEAN	4.5, 3.1	5.5, 4.3		0.5, 0.4	0.4, 0.4	
		SD, SE	3.47, 0.96	4.08, 2.04		0.53, 0.11	0.17, 0.06	
		MEDIAN	3.8	4.8		0.3	0.3	
		MIN, MAX	0.3, 11.3	1.8, 10.5		0.3, 2.8	0.3, 0.7	
		5%, 95%	0.3, 11.3	1.8, 10.5		0.3, 1.0	0.3, 0.7	
		# of BLQ/ALQ Values	1/0	0/0		13/0	3/0	
	Week 6	N	9	4	0.3961	24	6	0.1665
		MEAN, GEO MEAN	5.5, 3.8	3.5, 3.1		0.4, 0.4	0.6, 0.5	
		SD, SE	4.02, 1.34	1.87, 0.94		0.16, 0.03	0.31, 0.13	
		MEDIAN	4.5	3.3		0.3	0.5	
		MIN, MAX	0.3, 13.9	1.5, 5.8		0.3, 0.9	0.3, 1.1	
		5%, 95%	0.3, 13.9	1.5, 5.8		0.3, 0.7	0.3, 1.1	
		# of BLQ/ALQ Values	1/0	0/0		10/0	2/0	

NOTE: AM refers to biomarker collection before noon, PM refers to biomarker collection at noon or after.

* P-value from Wilcoxon rank-sum test.

PM3006438638

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

TABLE 14.2.1-4
Statistical Comparison Between AM and PM for Smokers and Non-Smokers of Selected Biomarkers of Exposure by Timepoint and Overall
(Page 3 of 9)

Biomarker: Carboxyhemoglobin (% saturation) Analytical Lab: CCLS

Gender	Timepoint	Statistic	Smokers			Non-Smokers		
			AM	PM	P-value ^a	AM	PM	P-value ^a
Overall	Week 1	N	34	16	0.9585	43	22	0.9400
		MEAN, GEO MEAN	4.5, 3.3	4.3, 3.3		0.4, 0.4	0.4, 0.4	
		SD, SE	3.21, 0.55	3.08, 0.77		0.17, 0.03	0.16, 0.03	
		MEDIAN	3.7	4.2		0.3	0.3	
		MIN, MAX	0.3, 14.8	0.9, 11.4		0.3, 1.0	0.3, 0.8	
		5%, 95%	0.8, 11.3	0.9, 11.4		0.3, 0.7	0.3, 0.7	
		# of BLQ/ALQ Values	1/0	0/0		25/0	14/0	
	Week 2	N	34	15	0.5875	51	14	0.8503
		MEAN, GEO MEAN	4.2, 2.9	3.6, 2.5		0.4, 0.3	0.4, 0.4	
		SD, SE	3.12, 0.54	2.81, 0.73		0.13, 0.02	0.24, 0.07	
		MEDIAN	3.6	2.6		0.3	0.3	
		MIN, MAX	0.3, 13.3	0.3, 9.8		0.3, 0.9	0.3, 1.1	
		5%, 95%	0.3, 10.1	0.3, 9.8		0.3, 0.7	0.3, 1.1	
		# of BLQ/ALQ Values	2/0	1/0		37/0	10/0	
	Week 3	N	37	9	0.4974	51	14	0.1438
		MEAN, GEO MEAN	4.8, 3.7	4.5, 3.3		0.5, 0.4	0.6, 0.4	
		SD, SE	2.96, 0.49	3.49, 1.16		0.48, 0.07	0.58, 0.16	
		MEDIAN	4.1	3.1		0.3	0.4	
		MIN, MAX	0.3, 11.3	0.7, 10.5		0.3, 2.8	0.3, 2.5	
		5%, 95%	0.3, 10.4	0.7, 10.5		0.3, 1.6	0.3, 2.5	
		# of BLQ/ALQ Values	1/0	0/0		33/0	5/0	
	Week 6	N	31	10	0.3387	54	11	0.0194
		MEAN, GEO MEAN	4.9, 3.8	4.0, 2.7		0.4, 0.4	0.5, 0.5	
		SD, SE	2.92, 0.52	3.14, 0.99		0.19, 0.03	0.25, 0.08	
		MEDIAN	4.5	3.3		0.3	0.4	
		MIN, MAX	0.3, 13.9	0.3, 9.2		0.3, 1.3	0.3, 1.1	
		5%, 95%	0.4, 9.8	0.3, 9.2		0.3, 0.8	0.3, 1.1	
		# of BLQ/ALQ Values	1/0	1/0		31/0	3/0	

NOTE: AM refers to biomarker collection before noon, PM refers to biomarker collection at noon or after.

^a P-value from Wilcoxon rank-sum test.

PM3006438639

Final Draft: 22 October 2003

Page 670 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

TABLE 14.2.1-4
Statistical Comparison Between AM and PM for Smokers and Non-Smokers of Selected Biomarkers of Exposure by Timepoint and Overall
(Page 4 of 9)

Biomarker: Acetonitrile (nL/L @20 °C and 1 atm)			Analytical Lab: Madison					
Gender	Timepoint	Statistic	Smokers		P-value*	Non-Smokers		P-value*
			AM	PM		AM	PM	
Female	Week 1	N	24	8	0.3592	23	12	0.1220
		MEAN, GEO MEAN	9197.406, 1311.823	16781.718, 3342.768		22989.985, 9938.599	38431.551, 21016.813	
		SD, SE	13705.8829, 2797.7016	19269.0303, 6812.6310		19137.6796, 3990.4821	27084.6769, 7818.6727	
		MEDIAN	439.902	7976.816		25182.623	37326.402	
		MIN, MAX	27.047, 59118.236	360.626, 43336.359		67.737, 54497.370	117.403, 90418.051	
		5%, 95%	27.047, 22265.091	360.626, 43336.359		671.507, 51712.349	117.403, 90418.051	
		# of BLQ/ALQ Values	3/8	0/4		0/0	0/0	
	Week 3	N	24	5	0.8064	28	7	0.3753
		MEAN, GEO MEAN	10294.955, 2054.833	8400.828, 1671.098		27303.463, 20657.012	36892.985, 33259.160	
		SD, SE	13820.7579, 2821.1504	13842.1107, 6190.3801		14080.9775, 2661.0546	18550.9475, 7011.5991	
		MEDIAN	722.772	360.626		28995.329	31028.322	
		MIN, MAX	27.047, 49646.042	360.626, 32326.622		703.834, 51460.152	17025.081, 64440.436	
		5%, 95%	360.626, 32770.330	360.626, 32326.622		2753.207, 44229.194	17025.081, 64440.436	
		# of BLQ/ALQ Values	1/11	0/3		0/0	0/0	
	Week 6	N	22	6	0.5795	30	5	1.0000
		MEAN, GEO MEAN	9807.737, 2250.643	10016.216, 1000.994		26894.960, 20724.486	27731.250, 26969.413	
		SD, SE	12195.4292, 2600.0742	16074.6976, 6562.4678		13112.2031, 2393.9498	7200.1256, 3219.9940	
		MEDIAN	2276.319	360.626		29198.741	29717.322	
		MIN, MAX	27.047, 37095.541	27.047, 38261.231		285.948, 58955.534	20243.545, 37028.299	
		5%, 95%	360.626, 32905.616	27.047, 38261.231		3549.774, 42384.015	20243.545, 37028.299	
		# of BLQ/ALQ Values	1/9	1/3		0/0	0/0	

NOTE: AM refers to biomarker collection before noon, PM refers to biomarker collection at noon or after.

* P-value from Wilcoxon rank-sum test.

PM3006438640

Final Draft: 22 October 2003

Page 671 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

TABLE 14.2.1-4
Statistical Comparison Between AM and PM for Smokers and Non-Smokers of Selected Biomarkers of Exposure by Timepoint and Overall
(Page 5 of 9)

Biomarker: Acetonitrile (nL/L @20 °C and 1 atm)		Analytical Lab: Madison						
Gender	Timepoint	Statistic	Smokers			Non-Smokers		
			AM	PM	P-value*	AM	PM	P-value*
Male	Week 1	N	10	8	0.7558	20	10	0.8603
		MEAN, GEO MEAN	16904.230, 8326.873	14316.314, 6254.584		17097.365, 7162.784	16468.872, 6236.335	
		SD, SE	20277.1984, 6412.2131	14995.5085, 5301.7129		15793.3208, 3531.4939	16455.2281, 5203.6000	
		MEDIAN	8240.636	9172.766		12584.867	8762.168	
		MIN, MAX	1283.024, 61266.718	278.352, 38265.077		27.047, 48597.939	27.047, 49048.904	
		5%, 95%	1283.024, 61266.718	278.352, 38265.077		59.975, 47313.460	27.047, 49048.904	
		# of BLQ/ALQ Values	0/0	0/0		1/0	1/0	
	Week 3	N	13	4	0.0793	23	7	0.5238
		MEAN, GEO MEAN	26388.561, 16738.102	11478.097, 9917.403		19812.928, 11507.278	25819.812, 9693.183	
		SD, SE	15238.0199, 4226.2663	6763.4827, 3381.7413		13098.5933, 2731.2455	18759.8474, 7090.5558	
		MEDIAN	29314.866	10610.769		19087.935	22947.667	
		MIN, MAX	149.199, 55212.198	4330.705, 20360.146		189.826, 41703.996	27.047, 48358.890	
		5%, 95%	149.199, 55212.198	4330.705, 20360.146		555.984, 37842.197	27.047, 48358.890	
		# of BLQ/ALQ Values	0/0	0/0		0/0	1/0	
	Week 6	N	10	4	1.0000	24	6	0.6974
		MEAN, GEO MEAN	19910.429, 13629.841	22844.579, 10705.685		24644.697, 16418.958	21592.468, 8033.725	
		SD, SE	16156.1257, 5109.0155	23809.0191, 11904.5095		14596.3978, 2979.4772	20263.5199, 8272.5473	
		MEDIAN	18634.588	19767.097		26642.053	19428.599	
		MIN, MAX	1827.506, 57117.622	2668.716, 49175.407		143.554, 47862.018	178.106, 49916.584	
		5%, 95%	1827.506, 57117.622	2668.716, 49175.407		2225.726, 46880.251	178.106, 49916.584	
		# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	

NOTE: AM refers to biomarker collection before noon, PM refers to biomarker collection at noon or after.

* P-value from Wilcoxon rank-sum test.

PM3006438641

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

TABLE 14.2.1-4
Statistical Comparison Between AM and PM for Smokers and Non-Smokers of Selected Biomarkers of Exposure by Timepoint and Overall
(Page 6 of 9)

Biomarker: Acetonitrile (nL/L @20 °C and 1 atm)		Analytical Lab. Madison						
Gender	Timepoint	Statistic	AM	Smokers PM	P-value*	AM	Non-Smokers PM	P-value*
Overall	Week 1	N	34	16	0.4829	43	22	0.2386
		MEAN, GEO MEAN	11464.119, 2259.103	15549.016, 4572.485		20249.232, 8534.252	28448.515, 12098.504	
		SD, SE	15992.7265, 2742.7300	16728.0971, 4182.0243		17706.6862, 2700.2443	25011.8052, 5332.5348	
		MEDIAN	2817.108	9172.766		16827.867	27302.458	
		MIN, MAX	27.047, 61266.718	278.352, 43336.359		27.047, 54497.370	27.047, 90418.051	
		5%, 95%	27.047, 59118.236	278.352, 43336.359		92.902, 50115.663	117.403, 74719.187	
		# of BLQ/ALQ Values	3/8	0/4		1/0	1/0	
	Week 3	N	37	9	0.5092	51	14	0.2539
		MEAN, GEO MEAN	15949.465, 4293.712	9768.503, 3587.513		23925.378, 15866.301	31356.399, 17955.142	
		SD, SE	16127.7100, 2651.3792	10751.1263, 3583.7088		14026.0527, 1964.0402	18822.1847, 5030.4405	
		MEDIAN	14371.511	8593.639		25973.434	28028.074	
		MIN, MAX	27.047, 55212.198	360.626, 32326.622		189.826, 51460.152	27.047, 64440.436	
		5%, 95%	149.199, 49646.042	360.626, 32326.622		571.554, 43507.242	27.047, 64440.436	
		# of BLQ/ALQ Values	1/11	0/3		0/0	1/0	
	Week 6	N	32	10	0.9405	54	11	0.7068
		MEAN, GEO MEAN	12964.828, 3951.292	15147.561, 2582.882		25894.843, 18686.737	24382.823, 13931.158	
		SD, SE	14112.6511, 2494.7878	19400.8827, 6135.0978		13704.2502, 1864.9122	15372.6860, 4635.0392	
		MEDIAN	8205.296	2693.761		28847.657	28310.649	
		MIN, MAX	27.047, 57117.622	27.047, 49175.407		143.554, 58955.534	178.106, 49916.584	
		5%, 95%	360.626, 37095.541	27.047, 49175.407		2275.726, 46880.251	178.106, 49916.584	
		# of BLQ/ALQ Values	1/9	1/3		0/0	0/0	

NOTE: AM refers to biomarker collection before noon, PM refers to biomarker collection at noon or after.

* P-value from Wilcoxon rank-sum test.

PM3006438642

Final Draft: 22 October 2003

Page 673 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

TABLE 14.2.1-4
Statistical Comparison Between AM and PM for Smokers and Non-Smokers of Selected Biomarkers of Exposure by Timepoint and Overall
(Page 7 of 9)

Biomarker: Carbon monoxide (ppm)		Analytical Lab: CRF						
Gender	Timepoint	Statistic	AM	Smokers PM	P-value ^a	AM	Non-Smokers PM	P-value ^a
Female	Week 1	N	23	9	0.6751	23	12	0.2026
		MEAN, GEO MEAN	25.3, 21.9	29.5, 24.7		5.2, 5.1	6.0, 5.8	
		SD, SE	13.98, 2.92	17.31, 5.77		1.14, 0.24	1.61, 0.46	
		MEDIAN	22.8	27.2		4.8	5.7	
		MIN, MAX	7.8, 66.5	8.4, 54.7		3.7, 8.1	4.0, 9.6	
		5%, 95%	9.6, 42.2	8.4, 54.7		4.0, 6.9	4.0, 9.6	
		# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
	Week 2	N	22	9	0.3723	27	8	0.5818
		MEAN, GEO MEAN	27.2, 22.4	20.8, 17.2		4.4, 4.3	4.5, 4.2	
		SD, SE	18.64, 3.97	13.86, 4.62		0.99, 0.19	2.06, 0.73	
		MEDIAN	23.0	18.0		4.4	3.8	
		MIN, MAX	6.5, 88.9	6.7, 50.1		2.2, 6.8	2.1, 8.6	
		5%, 95%	9.3, 55.6	6.7, 50.1		3.2, 5.7	2.1, 8.6	
		# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
	Week 3	N	24	5	0.0885	29	6	0.4433
		MEAN, GEO MEAN	28.3, 25.2	17.1, 14.1		4.6, 4.2	4.2, 4.1	
		SD, SE	12.86, 2.63	12.46, 5.57		1.41, 0.26	0.91, 0.37	
		MEDIAN	25.4	16.0		4.5	4.1	
		MIN, MAX	5.3, 60.7	7.2, 38.0		0.3, 7.4	3.0, 5.5	
		5%, 95%	12.4, 45.1	7.2, 38.0		3.1, 6.9	3.0, 5.5	
		# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
	Week 6	N	22	6	0.5566	30	5	0.7057
		MEAN, GEO MEAN	30.1, 27.9	26.9, 19.4		5.2, 4.5	5.4, 5.4	
		SD, SE	11.15, 2.38	20.87, 8.52		2.14, 0.39	0.79, 0.35	
		MEDIAN	28.6	19.5		4.9	5.5	
		MIN, MAX	10.1, 49.9	4.0, 54.0		0.4, 9.8	4.5, 6.5	
		5%, 95%	13.6, 47.9	4.0, 54.0		1.0, 9.0	4.5, 6.5	
		# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	

NOTE: AM refers to biomarker collection before noon, PM refers to biomarker collection at noon or after.

^a P-value from Wilcoxon rank-sum test.

PM3006438643

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

TABLE 14.2.1-4
Statistical Comparison Between AM and PM for Smokers and Non-Smokers of Selected Biomarkers of Exposure by Timepoint and Overall
(Page 8 of 9)

Biomarker: Carbon monoxide (ppm)		Analytical Lab: CRF						
Gender	Timepoint	Statistic	Smokers			Non-Smokers		
			AM	PM	P-value ^a	AM	PM	P-value ^a
Male	Week 1	N	11	7	0.9278	22	8	0.4524
		MEAN, GEO MEAN	27.0, 22.8	24.2, 21.8		6.1, 6.0	5.5, 5.3	
		SD, SE	17.63, 5.32	12.34, 4.67		1.29, 0.28	1.45, 0.51	
		MEDIAN	24.2	22.0		6.0	5.9	
		MIN, MAX	8.6, 71.4	11.6, 47.2		3.7, 9.1	3.6, 7.5	
		5%, 95%	8.6, 71.4	11.6, 47.2		4.5, 8.0	3.6, 7.5	
		# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
	Week 2	N	13	5	0.4301	24	6	0.2871
		MEAN, GEO MEAN	24.3, 20.4	19.5, 17.6		5.6, 4.9	6.9, 6.7	
		SD, SE	12.87, 3.57	9.48, 4.24		1.47, 0.30	1.97, 0.80	
		MEDIAN	21.8	16.6		5.9	6.6	
		MIN, MAX	4.5, 44.1	9.6, 32.0		0.1, 7.7	4.8, 9.6	
		5%, 95%	4.5, 44.1	9.6, 32.0		4.0, 7.5	4.8, 9.6	
		# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
	Week 3	N	14	3	0.9498	23	7	0.4029
		MEAN, GEO MEAN	25.4, 21.2	30.5, 22.9		6.1, 5.9	6.1, 6.1	
		SD, SE	14.94, 3.99	27.83, 16.07		1.78, 0.37	0.33, 0.12	
		MEDIAN	23.7	19.2		5.5	6.0	
		MIN, MAX	5.3, 55.1	10.1, 62.2		3.4, 10.6	5.8, 6.8	
		5%, 95%	5.3, 55.1	10.1, 62.2		4.0, 9.4	5.8, 6.8	
		# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
	Week 6	N	11	3	0.7555	25	5	0.6556
		MEAN, GEO MEAN	30.1, 24.9	24.0, 19.5		7.4, 7.0	7.1, 7.0	
		SD, SE	17.49, 5.27	19.50, 11.26		2.66, 0.53	0.94, 0.42	
		MEDIAN	26.1	14.4		6.5	7.0	
		MIN, MAX	5.0, 70.5	11.1, 46.4		4.5, 13.8	6.0, 8.6	
		5%, 95%	5.0, 70.5	11.1, 46.4		4.8, 13.3	6.0, 8.6	
		# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	

NOTE: AM refers to biomarker collection before noon, PM refers to biomarker collection at noon or after.

^a P-value from Wilcoxon rank-sum test.

PM3006438644

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

TABLE 14.2.1-4
Statistical Comparison Between AM and PM for Smokers and Non-Smokers of Selected Biomarkers of Exposure by Timepoint and Overall
(Page 9 of 9)

Biomarker: Carbon monoxide (ppm)		Analytical Lab: CRF						
Gender	Timepoint	Statistic	Smokers			Non-Smokers		
			AM	PM	P-value ^a	AM	PM	P-value ^a
Overall	Week 1	N	34	16	0.7948	45	20	0.8086
		MEAN, GEO MEAN	25.9, 22.2	27.2, 23.4		5.6, 5.5	5.8, 5.6	
		SD, SE	15.01, 2.57	15.10, 3.78		1.29, 0.19	1.52, 0.34	
		MEDIAN	23.5	23.6		5.7	5.7	
		MIN, MAX	7.8, 71.4	8.4, 54.7		3.7, 9.1	3.6, 9.6	
		5%, 95%	8.6, 66.5	8.4, 54.7		4.0, 8.0	3.7, 8.9	
		# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
	Week 2	N	35	14	0.2590	51	14	0.6897
		MEAN, GEO MEAN	26.2, 21.6	20.3, 17.3		5.0, 4.6	5.6, 5.1	
		SD, SE	16.58, 2.80	12.10, 3.23		1.35, 0.19	2.29, 0.61	
		MEDIAN	21.8	17.3		5.0	5.3	
		MIN, MAX	4.5, 88.9	6.7, 50.1		0.1, 7.7	2.1, 9.6	
		5%, 95%	6.5, 55.6	6.7, 50.1		3.2, 7.0	2.1, 9.6	
		# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
	Week 3	N	38	8	0.1778	52	13	0.6935
		MEAN, GEO MEAN	27.2, 23.7	22.1, 16.9		5.3, 4.9	5.2, 5.1	
		SD, SE	13.53, 2.20	18.93, 6.69		1.75, 0.24	1.20, 0.33	
		MEDIAN	25.0	16.2		5.1	5.8	
		MIN, MAX	5.3, 60.7	7.2, 62.2		0.3, 30.6	3.0, 6.8	
		5%, 95%	5.3, 55.1	7.2, 62.2		3.2, 8.6	3.0, 6.8	
		# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
	Week 6	N	33	9	0.3658	55	10	0.5789
		MEAN, GEO MEAN	30.1, 26.8	25.9, 19.4		6.2, 5.5	6.2, 6.1	
		SD, SE	13.31, 2.32	19.22, 6.41		2.61, 0.35	1.21, 0.38	
		MEDIAN	28.0	14.8		5.7	6.3	
		MIN, MAX	5.0, 70.5	4.0, 54.0		0.4, 13.8	4.5, 8.6	
		5%, 95%	10.0, 49.9	4.0, 54.0		1.3, 11.6	4.5, 8.6	
		# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	

NOTE: AM refers to biomarker collection before noon, PM refers to biomarker collection at noon or after.

* P-value from Wilcoxon rank-sum test.

PM3006438645

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

14.2.2 Comparison Between Smokers and Non-Smokers by Gender

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-1
Statistical Comparison Between Smokers and Non-Smokers by Gender of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 1 of 14)

Biomarker: Acetonitrile ((ng/mL)/2) Analytical Lab: Madison

Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	0.0003	32	35	0.0001
	MEAN, GEO MEAN	477.23, 333.46	171.70, 106.37		221.90, 173.46	184.61, 90.50	
	SD, SE	377.102, 88.884	258.462, 47.189		248.932, 44.005	313.664, 53.019	
	MEDIAN	312.53	107.85		154.60	88.39	
	MIN, MAX	51.48, 1346.61	30.00, 1436.84		66.48, 1500.00	30.00, 1500.00	
	5%, 95%	51.48, 1346.61	30.00, 431.13		75.16, 386.20	30.00, 972.68	
Week 2	# of BLQ/ALQ Values	1/0	8/0	0.0010	0/1	8/1	0.0154
	N	17	30		31	35	
	MEAN, GEO MEAN	436.61, 318.33	164.07, 114.31		314.55, 212.48	192.29, 116.73	
	SD, SE	360.287, 87.383	143.259, 26.155		313.375, 56.284	201.926, 34.132	
	MEDIAN	285.73	112.33		179.28	95.44	
	MIN, MAX	54.06, 1500.00	30.00, 688.37		30.00, 1500.00	30.00, 756.74	
Week 3	5%, 95%	54.06, 1500.00	30.00, 371.86	0.0001	48.66, 1002.96	30.00, 664.01	0.0014
	# of BLQ/ALQ Values	0/1	7/0		1/1	5/0	
	N	17	30		29	35	
	MEAN, GEO MEAN	820.39, 583.11	234.01, 153.58		383.39, 251.66	182.84, 118.86	
	SD, SE	694.688, 168.487	216.278, 39.487		429.385, 79.735	221.687, 37.472	
	MEDIAN	429.35	150.45		239.93	109.58	
Week 6	MIN, MAX	166.78, 2000.00	30.00, 896.92	0.0012	46.59, 2000.00	30.00, 1168.91	0.0731
	5%, 95%	166.78, 2000.00	30.00, 722.48		67.97, 1389.35	30.00, 619.94	
	# of BLQ/ALQ Values	0/4	6/0		0/1	4/0	
	N	14	30		28	35	
	MEAN, GEO MEAN	477.27, 375.66	203.58, 125.40		420.84, 251.72	242.70, 141.68	
	SD, SE	261.951, 70.009	224.030, 40.907		485.955, 91.837	241.581, 40.835	
Overall ^b	MEDIAN	509.88	108.47	<.0001	173.79	150.96	0.0127
	MIN, MAX	31.68, 1060.80	30.00, 886.61		49.12, 1500.00	30.00, 947.36	
	5%, 95%	31.68, 1060.80	30.00, 744.35		97.44, 1460.56	30.00, 670.92	
	# of BLQ/ALQ Values	0/0	6/0		0/1	7/0	
	N	18	30		32	35	
	MEAN, GEO MEAN	556.01, 495.30	193.34, 167.20		326.87, 258.33	200.61, 153.31	
Overall ^b	SD, SE	278.491, 65.641	105.774, 19.312	<.0001	230.694, 40.781	157.950, 26.699	0.0127
	MEDIAN	472.90	153.90		253.44	156.31	
	MIN, MAX	204.49, 1084.24	41.94, 452.36		82.80, 951.72	30.00, 701.92	
	5%, 95%	204.49, 1084.24	83.94, 382.94		85.41, 740.98	40.12, 599.86	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-1
Statistical Comparison Between Smokers and Non-Smokers by Gender of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 2 of 14)

Biomarker: Acetonitrile ((nmol/L)/2) Analytical Lab: Madaion

Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	0.0003	32	35	0.0001
	MEAN, GEO MEAN	11634.8, 8129.7	4186.1, 2593.3		5409.8, 4228.9	4500.7, 2206.4	
	SD, SE	9193.74, 2166.99	6301.32, 1150.46		6068.97, 1072.85	7647.13, 1292.60	
	MEDIAN	7619.5	2629.3		3769.2	2154.9	
	MIN, MAX	1255.1, 32830.4	731.4, 35030.2		1620.8, 36570.0	731.4, 36570.0	
	5%, 95%	1255.1, 32830.4	731.4, 10510.9		1832.4, 9415.6	731.4, 23713.9	
Week 2	# of BLQ/ALQ Values	1/0	8/0	0.0010	0/1	8/1	0.0154
	N	17	30		31	35	
	MEAN, GEO MEAN	10644.6, 7760.9	3999.9, 2786.9		7668.8, 5180.2	4688.1, 2845.8	
	SD, SE	8783.81, 2130.39	3492.67, 637.67		7640.09, 1372.20	4922.96, 832.13	
	MEDIAN	6966.1	2738.5		4370.8	2326.8	
	MIN, MAX	1318.0, 36570.0	731.4, 16782.5		731.4, 36570.0	731.4, 18449.3	
Week 3	5%, 95%	1318.0, 36570.0	731.4, 9065.9	0.0001	1186.3, 24452.2	731.4, 16188.6	0.0014
	# of BLQ/ALQ Values	0/1	7/0		1/1	5/0	
	N	17	30		29	35	
	MEAN, GEO MEAN	20001.2, 14216.3	5705.1, 3744.2		9347.0, 6135.5	4457.7, 2897.8	
	SD, SE	16936.49, 4107.70	5272.86, 962.69		10468.41, 1943.94	5404.72, 913.56	
	MEDIAN	10467.6	3668.0		5849.5	2671.6	
Week 6	MIN, MAX	4066.1, 48760.0	731.4, 21866.9	0.0012	1135.9, 48760.0	731.4, 28498.0	0.0731
	5%, 95%	4066.1, 48760.0	731.4, 17614.1		1657.1, 33872.4	731.4, 15114.1	
	# of BLQ/ALQ Values	0/4	6/0		0/1	4/0	
	N	14	30		28	35	
	MEAN, GEO MEAN	11635.7, 9158.6	4963.4, 3057.3		10260.1, 6136.8	5917.0, 3454.2	
	SD, SE	6386.36, 1706.83	5461.86, 997.20		11847.57, 2238.98	5889.73, 995.55	
Overall ^b	MEDIAN	12430.9	2644.5	<.0001	4237.0	3680.4	0.0127
	MIN, MAX	772.4, 25862.3	731.4, 21615.6		1197.5, 36570.0	731.4, 23096.6	
	5%, 95%	772.4, 25862.3	731.4, 18147.3		2375.6, 35608.5	731.4, 16357.0	
	# of BLQ/ALQ Values	0/0	6/0		0/1	7/0	
	N	18	30		32	35	
	MEAN, GEO MEAN	13555.4, 12075.3	4713.6, 4076.3		7969.0, 6298.0	4890.9, 3737.6	
Overall ^b	SD, SE	6789.62, 1600.33	2578.76, 470.82	<.0001	5624.31, 994.25	3850.84, 650.91	0.0127
	MEDIAN	11529.4	3752.0		6178.8	3810.7	
	MIN, MAX	4985.5, 26433.8	1022.5, 11028.6		2018.6, 23202.8	731.4, 17112.8	
	5%, 95%	4985.5, 26433.8	2046.5, 9336.2		2082.3, 18065.1	978.1, 14624.7	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-1
Statistical Comparison Between Smokers and Non-Smokers by Gender of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 3 of 14)

Biomarker: Acetonitrile ((ng/mL)/cigarette per day) ²		Analytical Lab: Madison					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	38.45, 26.28			17.29, 13.14		
	SD, SE	31.993, 7.541			16.633, 2.940		
	MEDIAN	33.25			11.57		
	MIN, MAX	5.47, 116.91			3.39, 88.24		
	5%, 95%	5.47, 116.91			4.18, 53.45		
	# of BLQ/ALQ Values	1/0			0/1		
Week 2	N	17		NA	31		NA
	MEAN, GEO MEAN	40.21, 23.17			27.93, 17.33		
	SD, SE	54.195, 13.144			34.908, 6.270		
	MEDIAN	25.98			13.65		
	MIN, MAX	6.76, 205.14			3.93, 174.28		
	5%, 95%	6.76, 205.14			4.11, 100.00		
	# of BLQ/ALQ Values	0/1			1/1		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	103.43, 54.84			29.62, 18.21		
	SD, SE	112.492, 27.283			35.787, 6.646		
	MEDIAN	35.03			14.37		
	MIN, MAX	9.05, 333.33			4.25, 158.87		
	5%, 95%	9.05, 333.33			4.89, 100.00		
	# of BLQ/ALQ Values	0/4			0/1		
Week 6	N	14		NA	28		NA
	MEAN, GEO MEAN	41.76, 29.28			50.12, 18.48		
	SD, SE	38.051, 10.170			131.352, 24.823		
	MEDIAN	31.82			14.19		
	MIN, MAX	3.17, 149.45			4.87, 703.19		
	5%, 95%	3.17, 149.45			5.17, 127.61		
	# of BLQ/ALQ Values	0/0			0/1		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	56.35, 42.29			30.71, 20.49		
	SD, SE	43.360, 10.220			44.995, 7.954		
	MEDIAN	40.20			22.09		
	MIN, MAX	8.68, 143.31			4.35, 264.63		
	5%, 95%	8.68, 143.31			7.10, 55.99		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-1
Statistical Comparison Between Smokers and Non-Smokers by Gender of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 4 of 14)

Biomarker: Acetonitrile ((nmol/L)/cigarette per day)/2)		Analytical Lab: Madison					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	937.3, 640.7			421.5, 320.2		
	SD, SE	779.97, 183.84			405.51, 71.68		
	MEDIAN	810.6			282.1		
	MIN, MAX	133.3, 2850.2			82.7, 2151.2		
	5%, 95%	133.3, 2850.2			101.8, 1303.1		
	# of BLQ/ALQ Values	1/0			0/1		
Week 2	N	17		NA	31		NA
	MEAN, GEO MEAN	980.3, 564.9			681.0, 422.5		
	SD, SE	1321.27, 320.46			851.05, 152.85		
	MEDIAN	633.3			332.9		
	MIN, MAX	164.7, 5001.3			95.9, 4249.0		
	5%, 95%	164.7, 5001.3			100.1, 2438.0		
	# of BLQ/ALQ Values	0/1			1/1		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	2521.5, 1337.1			722.2, 443.9		
	SD, SE	2742.59, 665.18			872.48, 162.02		
	MEDIAN	854.1			350.4		
	MIN, MAX	220.7, 8126.7			103.6, 3873.2		
	5%, 95%	220.7, 8126.7			119.3, 2438.0		
	# of BLQ/ALQ Values	0/4			0/1		
Week 6	N	14		NA	28		NA
	MEAN, GEO MEAN	1018.0, 713.8			1221.9, 450.4		
	SD, SE	927.67, 247.93			3202.36, 605.19		
	MEDIAN	775.9			345.9		
	MIN, MAX	77.2, 3643.5			118.8, 17143.8		
	5%, 95%	77.2, 3643.5			126.1, 3111.1		
	# of BLQ/ALQ Values	0/0			0/1		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	1373.8, 1031.0			748.7, 499.4		
	SD, SE	1057.14, 249.17			1096.97, 193.92		
	MEDIAN	980.1			538.5		
	MIN, MAX	211.5, 3493.7			106.1, 6451.6		
	5%, 95%	211.5, 3493.7			173.0, 1364.9		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-1
Statistical Comparison Between Smokers and Non-Smokers by Gender of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 5 of 14)

Biomarker: 3-Aminobiphenyl-Hb adduct (pg/g hemoglobin) Analytical Lab: Harrogate

Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	4.79, 3.24	0.51, 0.50		3.22, 2.43	0.67, 0.57	
	SD, SE	4.325, 1.019	0.022, 0.004		2.592, 0.466	0.692, 0.117	
	MEDIAN	2.88	0.50		2.03	0.50	
	MIN, MAX	0.50, 15.03	0.50, 0.62		0.50, 10.41	0.50, 4.59	
	5%, 95%	0.50, 15.03	0.50, 0.53		0.95, 9.39	0.50, 0.97	
	# of BLQ/ALQ Values	1/0	27/0		1/0	26/0	
Week 6	N	14	30	<.0001	28	35	<.0001
	MEAN, GEO MEAN	4.70, 3.32	0.59, 0.55		5.70, 2.76	0.59, 0.56	
	SD, SE	3.885, 1.038	0.385, 0.070		11.736, 2.218	0.292, 0.049	
	MEDIAN	3.15	0.50		2.70	0.50	
	MIN, MAX	0.50, 12.65	0.50, 2.46		0.50, 63.34	0.50, 1.84	
	5%, 95%	0.50, 12.65	0.50, 1.35		0.50, 13.54	0.50, 1.45	
	# of BLQ/ALQ Values	1/0	28/0		2/0	31/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	4.62, 3.23	0.55, 0.53		4.26, 2.71	0.63, 0.58	
	SD, SE	3.929, 0.926	0.197, 0.036		5.775, 1.021	0.370, 0.063	
	MEDIAN	2.97	0.50		2.36	0.50	
	MIN, MAX	0.50, 13.35	0.50, 1.48		0.50, 32.18	0.50, 2.55	
	5%, 95%	0.50, 13.35	0.50, 0.99		0.81, 11.98	0.50, 1.17	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438651

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-1
Statistical Comparison Between Smokers and Non-Smokers by Gender of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 6 of 14)

Biomarker: 3-Aminobiphenyl-Hb adduct ((pg/g hemoglobin)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18		NA	31		NA
	MEAN, GEO MEAN	0.35, 0.25			0.23, 0.19		
	SD, SE	0.310, 0.073			0.146, 0.026		
	MEDIAN	0.24			0.17		
	MIN, MAX	0.08, 1.17			0.06, 0.57		
	5%, 95%	0.08, 1.17			0.06, 0.47		
	# of BLQ/ALQ Values	1/0			1/0		
Week 6	N	14		NA	28		NA
	MEAN, GEO MEAN	0.46, 0.26			1.35, 0.20		
	SD, SE	0.670, 0.179			5.945, 1.124		
	MEDIAN	0.21			0.17		
	MIN, MAX	0.06, 2.60			0.03, 31.67		
	5%, 95%	0.06, 2.60			0.05, 0.66		
	# of BLQ/ALQ Values	1/0			2/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	0.38, 0.26			0.73, 0.22		
	SD, SE	0.434, 0.102			2.793, 0.494		
	MEDIAN	0.23			0.22		
	MIN, MAX	0.07, 1.82			0.05, 16.01		
	5%, 95%	0.07, 1.82			0.06, 0.57		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438652

Final Draft: 22 October 2003

Page 683 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-1
Statistical Comparison Between Smokers and Non-Smokers by Gender of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 7 of 14)

Biomarker: 4-Aminobiphenyl-Hb adduct (pg/g hemoglobin) Analytical Lab: Harrogate

Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	45.39, 37.62	6.28, 5.66		28.01, 24.04	8.13, 7.35	
	SD, SE	27.734, 6.537	3.023, 0.552		14.440, 2.594	4.064, 0.687	
	MEDIAN	38.12	5.39		25.56	6.80	
	MIN, MAX	12.37, 100.50	2.90, 13.87		5.35, 67.83	2.49, 23.25	
	5%, 95%	12.37, 100.50	3.12, 13.59		5.37, 50.52	2.95, 17.37	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Week 6	N	14	30	<.0001	28	35	<.0001
	MEAN, GEO MEAN	44.70, 37.31	8.92, 7.86		66.16, 38.07	8.71, 8.05	
	SD, SE	25.972, 6.941	5.287, 0.965		146.613, 27.707	3.907, 0.660	
	MEDIAN	41.52	7.43		37.63	7.53	
	MIN, MAX	9.56, 97.75	4.11, 27.86		7.27, 808.80	4.09, 22.67	
	5%, 95%	9.56, 97.75	4.31, 20.64		7.32, 90.32	4.36, 15.91	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	43.73, 36.74	7.60, 6.81		44.63, 31.28	8.43, 7.84	
	SD, SE	25.307, 5.965	3.989, 0.728		68.194, 12.055	3.697, 0.625	
	MEDIAN	41.27	6.49		32.62	7.17	
	MIN, MAX	12.37, 99.13	3.62, 20.87		6.31, 408.68	4.07, 22.96	
	5%, 95%	12.37, 99.13	3.83, 15.04		6.35, 79.08	4.71, 16.35	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438653

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-1
Statistical Comparison Between Smokers and Non-Smokers by Gender of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 8 of 14)

Biomarker: 4-Aminobiphenyl-Hb adduct ((pg/g hemoglobin)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value*	Smokers	Non-Smokers	P-value*
Week 1	N	18		NA	31		NA
	MEAN, GEO MEAN	3.96, 2.96			2.12, 1.84		
	SD, SE	3.964, 0.934			1.247, 0.224		
	MEDIAN	2.86			1.75		
	MIN, MAX	0.71, 18.14			0.59, 6.43		
	5%, 95%	0.71, 18.14			0.90, 4.79		
	# of BLQ/ALQ Values	0/0			0/0		
Week 6	N	14		NA	28		NA
	MEAN, GEO MEAN	5.19, 2.91			16.89, 2.79		
	SD, SE	9.231, 2.467			75.953, 14.354		
	MEDIAN	2.07			2.43		
	MIN, MAX	1.08, 36.66			0.95, 404.40		
	5%, 95%	1.08, 36.66			1.29, 6.49		
	# of BLQ/ALQ Values	0/0			0/0		
Overall*	N	18		NA	32		NA
	MEAN, GEO MEAN	4.26, 2.92			8.66, 2.46		
	SD, SE	5.997, 1.414			35.599, 6.293		
	MEDIAN	2.63			1.97		
	MIN, MAX	0.90, 27.40			0.93, 203.63		
	5%, 95%	0.90, 27.40			1.16, 6.43		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438654

Final Draft: 22 October 2003

Page 685 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-1
Statistical Comparison Between Smokers and Non-Smokers by Gender of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 9 of 14)

Biomarker: Carboxyhemoglobin (% saturation) Analytical Lab: CCLS							
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	4.4, 3.3	0.5, 0.4		4.5, 3.4	0.3, 0.3	
	SD, SE	3.35, 0.79	0.20, 0.04		3.07, 0.54	0.08, 0.01	
	MEDIAN	4.0	0.4		3.8	0.3	
	MIN, MAX	0.3, 14.8	0.3, 1.0		0.8, 11.4	0.3, 0.7	
	5%, 95%	0.3, 14.8	0.3, 0.8		0.9, 11.3	0.3, 0.5	
	# of BLQ/ALQ Values	1/0	12/0		0/0	27/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	3.7, 2.7	0.4, 0.4		4.2, 2.8	0.3, 0.3	
	SD, SE	2.69, 0.63	0.22, 0.04		3.21, 0.58	0.05, 0.01	
	MEDIAN	3.0	0.3		3.7	0.3	
	MIN, MAX	0.3, 8.6	0.3, 1.1		0.3, 13.3	0.3, 0.5	
	5%, 95%	0.3, 8.6	0.3, 0.9		0.3, 10.1	0.3, 0.5	
	# of BLQ/ALQ Values	1/0	17/0		2/0	30/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	4.7, 3.4	0.5, 0.4		4.8, 3.8	0.5, 0.4	
	SD, SE	3.52, 0.85	0.47, 0.09		2.78, 0.52	0.53, 0.09	
	MEDIAN	3.8	0.3		4.1	0.3	
	MIN, MAX	0.3, 11.3	0.3, 2.8		0.3, 9.7	0.3, 2.5	
	5%, 95%	0.3, 11.3	0.3, 1.0		0.7, 9.3	0.3, 2.2	
	# of BLQ/ALQ Values	1/0	16/0		0/0	22/0	
Week 6	N	13	30	<.0001	28	35	<.0001
	MEAN, GEO MEAN	4.9, 3.5	0.4, 0.4		4.6, 3.5	0.4, 0.4	
	SD, SE	3.55, 0.99	0.20, 0.04		2.72, 0.51	0.21, 0.03	
	MEDIAN	4.1	0.3		4.3	0.3	
	MIN, MAX	0.3, 13.9	0.3, 1.1		0.3, 9.8	0.3, 1.3	
	5%, 95%	0.3, 13.9	0.3, 0.9		0.4, 9.2	0.3, 0.8	
	# of BLQ/ALQ Values	1/0	12/0		1/0	22/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	4.2, 3.2	0.5, 0.4		4.4, 3.4	0.4, 0.4	
	SD, SE	3.00, 0.71	0.20, 0.04		2.89, 0.51	0.17, 0.03	
	MEDIAN	3.6	0.4		4.1	0.3	
	MIN, MAX	0.3, 12.2	0.3, 1.3		0.6, 11.0	0.3, 1.1	
	5%, 95%	0.3, 12.2	0.3, 0.8		0.7, 9.8	0.3, 0.9	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-1
Statistical Comparison Between Smokers and Non-Smokers by Gender of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 10 of 14)

Biomarker: Carboxyhemoglobin ((% saturation)/cigarette per day)		Analytical Lab: CCLS					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	0.4, 0.3			0.3, 0.3		
	SD, SE	0.67, 0.16			0.18, 0.03		
	MEDIAN	0.2			0.3		
	MIN, MAX	0.1, 3.0			0.1, 0.8		
	5%, 95%	0.1, 3.0			0.1, 0.8		
	# of BLQ/ALQ Values	1/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	0.4, 0.2			0.3, NA		
	SD, SE	0.97, 0.23			0.19, 0.03		
	MEDIAN	0.2			0.2		
	MIN, MAX	0.1, 4.3			0.0, 1.0		
	5%, 95%	0.1, 4.3			0.1, 0.5		
	# of BLQ/ALQ Values	1/0			2/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	0.5, 0.3			0.3, 0.3		
	SD, SE	0.51, 0.12			0.20, 0.04		
	MEDIAN	0.3			0.3		
	MIN, MAX	0.1, 2.3			0.1, 1.1		
	5%, 95%	0.1, 2.3			0.1, 0.6		
	# of BLQ/ALQ Values	1/0			0/0		
Week 6	N	13		NA	28		NA
	MEAN, GEO MEAN	0.8, 0.3			0.3, 0.3		
	SD, SE	1.88, 0.52			0.23, 0.04		
	MEDIAN	0.2			0.3		
	MIN, MAX	0.1, 7.0			0.1, 1.3		
	5%, 95%	0.1, 7.0			0.1, 0.7		
	# of BLQ/ALQ Values	1/0			1/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	0.5, 0.3			0.3, 0.3		
	SD, SE	0.93, 0.22			0.19, 0.03		
	MEDIAN	0.3			0.3		
	MIN, MAX	0.1, 4.2			0.1, 1.1		
	5%, 95%	0.1, 4.2			0.1, 0.7		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-1
Statistical Comparison Between Smokers and Non-Smokers by Gender of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 11 of 14)

Biomarker: 3-Aminobiphenyl-Hb adduct (pg/g hemoglobin)		Analytical Lab: INBIFO					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	2	4	0.7237	1	4	NA
	MEAN, GEO MEAN	0.70, 0.70	2.17, 1.23		0.70, 0.70	0.70, 0.70	
	SD, SE	0.000, 0.000	2.945, 1.473		NA, NA	0.000, 0.000	
	MEDIAN	0.70	0.70		0.70	0.70	
	MIN, MAX	0.70, 0.70	0.70, 6.59		0.70, 0.70	0.70, 0.70	
	5%, 95%	0.70, 0.70	0.70, 6.59		NA, NA	0.70, 0.70	
	# of BLQ/ALQ Values	2/0	3/0		1/0	4/0	
Week 6	N	2	4	1.0000	1	4	NA
	MEAN, GEO MEAN	0.70, 0.70	0.70, 0.70		0.70, 0.70	0.70, 0.70	
	SD, SE	0.000, 0.000	0.000, 0.000		NA, NA	0.000, 0.000	
	MEDIAN	0.70	0.70		0.70	0.70	
	MIN, MAX	0.70, 0.70	0.70, 0.70		0.70, 0.70	0.70, 0.70	
	5%, 95%	0.70, 0.70	0.70, 0.70		NA, NA	0.70, 0.70	
	# of BLQ/ALQ Values	2/0	4/0		1/0	4/0	
Overall [*]	N	3	4	0.5637	2	4	1.0000
	MEAN, GEO MEAN	0.70, 0.70	1.44, 1.06		0.70, 0.70	0.70, 0.70	
	SD, SE	0.000, 0.000	1.475, 0.738		0.000, 0.000	0.000, 0.000	
	MEDIAN	0.70	0.70		0.70	0.70	
	MIN, MAX	0.70, 0.70	0.70, 3.65		0.70, 0.70	0.70, 0.70	
	5%, 95%	0.70, 0.70	0.70, 3.65		0.70, 0.70	0.70, 0.70	

^a P-value from Wilcoxon rank-sum test.

^{*} Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438657

Final Draft: 22 October 2003

Page 688 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-1
Statistical Comparison Between Smokers and Non-Smokers by Gender of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 12 of 14)

Biomarker: 3-Aminobiphenyl-Hb adduct ((pg/g hemoglobin)/cigarette per day)		Analytical Lab: INBIFO					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	2		NA	1		NA
	MEAN, GEO MEAN	0.08, 0.07			0.06, 0.06		
	SD, SE	0.057, 0.040			NA, NA		
	MEDIAN	0.08			0.06		
	MIN, MAX	0.04, 0.12			0.06, 0.06		
	5%, 95%	0.04, 0.12			NA, NA		
	# of BLQ/ALQ Values	2/0			1/0		
Week 6	N	2		NA	1		NA
	MEAN, GEO MEAN	0.06, 0.05			0.18, 0.18		
	SD, SE	0.021, 0.015			NA, NA		
	MEDIAN	0.06			0.18		
	MIN, MAX	0.04, 0.07			0.18, 0.18		
	5%, 95%	0.04, 0.07			NA, NA		
	# of BLQ/ALQ Values	2/0			1/0		
Overall ^b	N	3		NA	2		NA
	MEAN, GEO MEAN	0.06, 0.05			0.12, 0.10		
	SD, SE	0.035, 0.020			0.085, 0.060		
	MEDIAN	0.04			0.12		
	MIN, MAX	0.04, 0.10			0.06, 0.18		
	5%, 95%	0.04, 0.10			0.06, 0.18		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., "<1.234" will be used as "1.234") for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438658

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-1
Statistical Comparison Between Smokers and Non-Smokers by Gender of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 13 of 14)

Biomarker: 4-Aminobiphenyl-Hb adduct (pg/g hemoglobin) Analytical Lab: INBIFO

Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	4	4	0.0304	3	4	0.0518
	MEAN, GEO MEAN	28.28, 27.74	9.64, 9.20		40.03, 37.23	11.21, 10.48	
	SD, SE	6.004, 3.002	3.405, 1.702		19.605, 11.319	4.996, 2.498	
	MEDIAN	29.75	9.06		29.87	9.68	
	MIN, MAX	19.77, 33.83	6.74, 13.71		27.59, 62.63	7.07, 18.39	
	5%, 95%	19.77, 33.83	6.74, 13.71		27.59, 62.63	7.07, 18.39	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Week 6	N	3	4	0.2159	4	4	0.0304
	MEAN, GEO MEAN	18.19, 18.13	13.06, 12.31		43.37, 39.47	9.54, 9.09	
	SD, SE	1.828, 1.055	4.998, 2.499		23.707, 11.853	3.683, 1.842	
	MEDIAN	17.44	12.85		33.69	8.14	
	MIN, MAX	16.85, 20.27	7.30, 19.24		27.83, 78.25	6.90, 14.99	
	5%, 95%	16.85, 20.27	7.30, 19.24		27.83, 78.25	6.90, 14.99	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Overall ^b	N	4	4	0.0304	4	4	0.0304
	MEAN, GEO MEAN	24.61, 24.24	11.35, 10.93		40.34, 39.14	10.38, 9.81	
	SD, SE	4.738, 2.369	3.433, 1.717		11.431, 5.715	4.315, 2.158	
	MEDIAN	25.46	11.54		39.06	8.91	
	MIN, MAX	18.31, 29.21	7.11, 15.22		29.19, 54.06	6.99, 16.69	
	5%, 95%	18.31, 29.21	7.11, 15.22		29.19, 54.06	6.99, 16.69	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438659

Final Draft: 22 October 2003

Page 690 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-1
Statistical Comparison Between Smokers and Non-Smokers by Gender of Blood and/or Plasma Biomarkers of Exposure by Timepoint and Overall
(Page 14 of 14)

Biomarker: 4-Aminobiphenyl-Hb adduct (tpg/g hemoglobin/cigarette per day)		Analytical Lab: INBIFO					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	4		NA	3		NA
	MEAN, GEO MEAN	3.32, 2.90			6.32, 3.30		
	SD, SE	1.924, 0.962			8.115, 4.685		
	MEDIAN	2.99			2.30		
	MIN, MAX	1.68, 5.64			1.00, 15.66		
	5%, 95%	1.68, 5.64			1.00, 15.66		
	# of BLQ/ALQ Values	0/0			0/0		
Week 6	N	3		NA	4		NA
	MEAN, GEO MEAN	1.30, 1.21			3.80, 3.44		
	SD, SE	0.636, 0.367			2.134, 1.067		
	MEDIAN	0.97			2.90		
	MIN, MAX	0.89, 2.03			2.43, 6.96		
	5%, 95%	0.89, 2.03			2.43, 6.96		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	4		NA	4		NA
	MEAN, GEO MEAN	2.67, 2.32			4.57, 3.42		
	SD, SE	1.545, 0.772			4.508, 2.254		
	MEDIAN	2.60			2.59		
	MIN, MAX	1.33, 4.17			1.81, 11.31		
	5%, 95%	1.33, 4.17			1.81, 11.31		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438660

Final Draft: 22 October 2003

Page 691 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 1 of 264)

Biomarker: NNAL (pg/24hr)		Analytical Lab: Madison					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	191274.750, 138941.078	104111.800, 9179.577		281919.984, 211578.900	12554.851, 11115.607	
	SD, SE	118708.1704, 27979.7841	5411.7101, 988.0386		201340.9792, 35592.3929	6518.8212, 1101.8819	
	MEDIAN	192779.000	8190.000		234058.500	11100.000	
	MIN, MAX	8460.000, 409840.000	3180.000, 22800.000		16500.000, 852355.000	3420.000, 30796.800	
	5%, 95%	8460.000, 409840.000	3900.000, 20100.000		23940.000, 671265.000	4800.000, 27840.000	
	# of BLQ/ALQ Values	1/0	29/0		1/0	32/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	229255.471, 150668.308	15485.700, 12411.461		307183.903, 256566.325	12785.229, 11917.008	
	SD, SE	184405.3931, 44724.8773	12690.8350, 2317.0189		164685.2029, 30581.2745	4916.9699, 831.1196	
	MEDIAN	162848.000	11400.000		286356.000	12180.000	
	MIN, MAX	6288.000, 573980.000	4500.000, 57240.000		45936.000, 781704.000	5640.000, 28440.000	
	5%, 95%	6288.000, 573980.000	4500.000, 52910.000		52452.000, 535470.000	5940.000, 20100.000	
	# of BLQ/ALQ Values	1/0	27/0		0/0	34/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	210260.875, 149953.882	12948.750, 11411.289		287126.995, 234337.908	12670.040, 11705.685	
	SD, SE	140301.9013, 33069.4753	7000.2068, 1278.0570		166377.3100, 29411.6310	5321.9122, 899.5673	
	MEDIAN	185850.500	10033.500		262596.375	11790.000	
	MIN, MAX	7374.000, 426577.000	3840.000, 32310.000		34476.000, 589956.000	5910.000, 28140.000	
	5%, 95%	7374.000, 426577.000	5280.000, 29095.000		53922.000, 588892.500	6450.000, 24998.400	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438661

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 2 of 264)

Biomarker: NNAL (pmol/24hr)		Analytical Lab: Madison					
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	914.293, 664.139	49.768, 43.878		1347.578, 1011.347	60.012, 53.133	
	SD, SE	567.4251, 133.7434	25.8680, 4.7228		962.4099, 170.1316	31.1599, 5.2670	
	MEDIAN	921.484	39.148		1118.800	53.058	
	MIN, MAX	40.439, 1959.035	15.200, 108.984		78.870, 4074.257	16.348, 147.209	
	5%, 95%	40.439, 1959.035	18.642, 96.078		114.433, 3208.647	22.944, 133.075	
	# of BLQ/ALQ Values	1/0	29/0		1/0	32/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	1095.841, 720.195	74.022, 59.327		1468.339, 1226.387	61.113, 56.963	
	SD, SE	881.4577, 213.7849	60.6622, 11.0754		787.1953, 146.1785	23.5031, 3.9727	
	MEDIAN	778.413	54.492		1368.782	58.220	
	MIN, MAX	30.057, 2743.624	21.510, 273.607		219.574, 3736.545	26.959, 135.943	
	5%, 95%	30.057, 2743.624	21.510, 252.910		250.721, 2559.547	28.393, 96.078	
	# of BLQ/ALQ Values	1/0	27/0		0/0	34/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	1005.047, 716.780	61.895, 54.546		1372.467, 1120.135	60.563, 55.953	
	SD, SE	670.6430, 158.0721	33.4610, 6.1091		795.2836, 140.5876	25.4387, 4.2999	
	MEDIAN	888.366	47.961		1255.211	56.357	
	MIN, MAX	35.248, 2039.038	18.355, 154.442		164.796, 2819.990	28.250, 134.509	
	5%, 95%	35.248, 2039.038	25.239, 139.074		257.747, 2814.907	30.831, 119.493	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 3 of 264)

Biomarker: NNAL ((pg/24hr)/cigarette per day) Analytical Lab: Madison

Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	14085.758, 10948.960			20419.190, 16021.124		
	SD, SE	11496.8277, 2709.8283			16442.9829, 2906.7362		
	MEDIAN	9920.500			14300.465		
	MIN, MAX	2820.000, 50956.800			5781.000, 85235.500		
	5%, 95%	2820.000, 50956.800			5852.273, 46530.000		
	# of BLQ/ALQ Values	1/0			1/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	17404.532, 14171.545			21914.687, 18561.087		
	SD, SE	9655.2960, 2341.7533			14064.9755, 2611.8004		
	MEDIAN	16640.000			16884.000		
	MIN, MAX	2096.000, 36162.000			7314.000, 64500.000		
	5%, 95%	2096.000, 36162.000			7826.000, 52113.600		
	# of BLQ/ALQ Values	1/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	15538.380, 12750.184			21374.985, 18123.410		
	SD, SE	9552.7621, 2251.6076			13308.0772, 2352.5579		
	MEDIAN	14099.908			15865.686		
	MIN, MAX	2458.000, 41763.200			6803.500, 62355.425		
	5%, 95%	2458.000, 41763.200			6936.783, 46530.000		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 4 of 264)

Biomarker: NNAL (pmol/24hr/cigarette per day) Analytical Lab: Madison

Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	67.330, 52.336			97.604, 76.581		
	SD, SE	54.9549, 12.9530			78.5975, 13.8942		
	MEDIAN	47.420			68.356		
	MIN, MAX	13.480, 243.574			27.633, 407.426		
	5%, 95%	13.480, 243.574			27.974, 222.413		
Week 3	# of BLQ/ALQ Values	1/0		NA	1/0		NA
	N	17			29		
	MEAN, GEO MEAN	83.194, 67.740			104.752, 88.722		
	SD, SE	46.1524, 11.1936			67.2306, 12.4844		
	MEDIAN	79.539			80.706		
	MIN, MAX	10.019, 172.854			34.961, 308.310		
Overall†	5%, 95%	10.019, 172.854		NA	37.408, 249.103		NA
	# of BLQ/ALQ Values	1/0			0/0		
	N	18			32		
	MEAN, GEO MEAN	74.274, 60.946			102.173, 86.630		
	SD, SE	45.6623, 10.7627			63.6126, 11.2452		
	MEDIAN	67.398			75.838		
	MIN, MAX	11.750, 199.629			32.521, 298.059		
	5%, 95%	11.750, 199.629			33.158, 222.413		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

† Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 5 of 264)

Biomarker: NNAL (pg/mg Creatinine)		Analytical Lab: Madison					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	160.048, 105.095	5.942, 5.166		252.415, 184.524	10.689, 9.434	
	SD, SE	171.2216, 40.3573	3.3379, 0.6094		181.5307, 32.0904	5.4597, 0.9229	
	MEDIAN	105.373	4.491		208.248	9.509	
	MIN, MAX	7.958, 767.052	1.932, 14.815		12.795, 813.359	2.285, 29.814	
	5%, 95%	7.958, 767.052	2.683, 11.788		13.730, 612.755	3.436, 20.782	
	# of BLQ/ALQ Values	1/0	29/0		1/0	32/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	153.041, 108.730	8.665, 6.794		270.188, 218.820	11.615, 10.332	
	SD, SE	106.2859, 25.7781	6.9510, 1.2691		171.0361, 31.7606	5.7724, 0.9757	
	MEDIAN	109.091	6.367		225.402	10.657	
	MIN, MAX	5.525, 368.503	2.158, 30.264		47.240, 724.324	3.259, 30.000	
	5%, 95%	5.525, 368.503	2.413, 29.578		52.222, 553.597	3.795, 23.715	
	# of BLQ/ALQ Values	1/0	27/0		0/0	34/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	155.884, 110.331	7.304, 6.332		260.848, 202.542	11.152, 10.111	
	SD, SE	125.4039, 29.5580	4.0261, 0.7351		177.8695, 31.4432	4.8999, 0.8282	
	MEDIAN	121.636	5.790		207.009	10.520	
	MIN, MAX	6.742, 522.399	2.364, 17.426		32.976, 768.842	3.348, 23.043	
	5%, 95%	6.742, 522.399	2.693, 16.420		34.373, 612.755	4.532, 21.741	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 6 of 264)

Biomarker: NNAL (pmol/mg Creatinine)		Analytical Lab: Madison					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	0.765, 0.502	0.028, 0.025		1.207, 0.882	0.051, 0.045	
	SD, SE	0.8185, 0.1929	0.0160, 0.0029		0.8678, 0.1534	0.0262, 0.0044	
	MEDIAN	0.504	0.022		0.996	0.045	
	MIN, MAX	0.038, 3.667	0.009, 0.071		0.061, 3.888	0.011, 0.143	
	5%, 95%	0.038, 3.667	0.013, 0.056		0.066, 2.929	0.016, 0.099	
	# of BLQ/ALQ Values	1/0	29/0		1/0	32/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	0.731, 0.519	0.041, 0.032		1.291, 1.046	0.056, 0.049	
	SD, SE	0.5080, 0.1232	0.0332, 0.0061		0.8175, 0.1518	0.0275, 0.0046	
	MEDIAN	0.521	0.031		1.077	0.051	
	MIN, MAX	0.026, 1.761	0.010, 0.145		0.226, 3.462	0.016, 0.143	
	5%, 95%	0.026, 1.761	0.012, 0.141		0.250, 2.646	0.018, 0.113	
	# of BLQ/ALQ Values	1/0	27/0		0/0	34/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	0.745, 0.527	0.035, 0.030		1.247, 0.968	0.054, 0.049	
	SD, SE	0.5996, 0.1413	0.0193, 0.0035		0.8503, 0.1503	0.0233, 0.0039	
	MEDIAN	0.582	0.028		0.990	0.051	
	MIN, MAX	0.032, 2.498	0.011, 0.084		0.158, 3.675	0.016, 0.110	
	5%, 95%	0.032, 2.498	0.013, 0.079		0.164, 2.929	0.022, 0.104	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438666

Final Draft: 22 October 2003

Page 697 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 7 of 264)

Biomarker: NNAL ((pg/mg Creatinine)/cigarette per day)		Analytical Lab: Madison					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value*	Smokers	Non-Smokers	P-value*
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	16.423, 8.282			17.616, 13.972		
	SD, SE	34.5325, 8.1394			12.0923, 2.1376		
	MEDIAN	6.962			14.081		
	MIN, MAX	2.653, 153.410			3.199, 51.694		
	5%, 95%	2.653, 153.410			4.430, 40.850		
	# of BLQ/ALQ Values	1/0			1/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	13.465, 10.227			19.709, 15.830		
	SD, SE	12.1015, 2.9350			15.4795, 2.8745		
	MEDIAN	12.019			13.056		
	MIN, MAX	1.842, 55.549			6.429, 69.200		
	5%, 95%	1.842, 55.549			6.641, 61.602		
	# of BLQ/ALQ Values	1/0			0/0		
Overall*	N	18		NA	32		NA
	MEAN, GEO MEAN	14.726, 9.379			19.095, 15.708		
	SD, SE	22.8841, 5.3938			12.7178, 2.2482		
	MEDIAN	9.583			14.886		
	MIN, MAX	2.248, 104.480			5.430, 60.447		
	5%, 95%	2.248, 104.480			5.699, 40.850		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 8 of 264)

Biomarker: NNAL ((pmol/mg Creatinine)/cigarette per day)		Analytical Lab: Madison					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	0.079, 0.040			0.084, 0.067		
	SD, SE	0.1650, 0.0389			0.0578, 0.0102		
	MEDIAN	0.034			0.067		
	MIN, MAX	0.013, 0.733			0.015, 0.247		
	5%, 95%	0.013, 0.733			0.021, 0.195		
	# of BLQ/ALQ Values	1/0			1/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	0.064, 0.049			0.094, 0.076		
	SD, SE	0.0580, 0.0141			0.0740, 0.0137		
	MEDIAN	0.057			0.063		
	MIN, MAX	0.009, 0.266			0.031, 0.331		
	5%, 95%	0.009, 0.266			0.032, 0.295		
	# of BLQ/ALQ Values	1/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	0.071, 0.045			0.092, 0.076		
	SD, SE	0.1095, 0.0258			0.0608, 0.0107		
	MEDIAN	0.046			0.072		
	MIN, MAX	0.011, 0.500			0.026, 0.289		
	5%, 95%	0.011, 0.500			0.028, 0.195		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438668

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 9 of 264)

Biomarker: NNAL (pg/mL)		Analytical Lab: Madison					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	121.7, 84.9	6.5, 6.2		166.0, 120.8	6.3, 6.2	
	SD, SE	83.64, 19.71	2.61, 0.48		116.66, 20.62	0.93, 0.16	
	MEDIAN	127.5	6.0		150.8	6.0	
	MIN, MAX	6.0, 333.0	6.0, 20.3		6.0, 484.5	6.0, 9.6	
	5%, 95%	6.0, 333.0	6.0, 6.0		11.4, 463.9	6.0, 9.6	
	# of BLQ/ALQ Values	1/0	29/0		1/0	32/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	122.7, 89.1	8.7, 7.1		183.8, 149.5	6.1, 6.1	
	SD, SE	81.19, 19.69	9.14, 1.67		118.10, 21.93	0.76, 0.13	
	MEDIAN	134.6	6.0		160.8	6.0	
	MIN, MAX	6.0, 290.8	6.0, 42.4		28.2, 485.1	6.0, 10.5	
	5%, 95%	6.0, 290.8	6.0, 40.7		45.6, 411.9	6.0, 6.0	
	# of BLQ/ALQ Values	1/0	27/0		0/0	34/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	122.7, 92.8	7.6, 6.9		171.2, 135.6	6.2, 6.2	
	SD, SE	68.42, 16.13	4.69, 0.86		112.66, 19.92	0.59, 0.10	
	MEDIAN	135.9	6.0		152.1	6.0	
	MIN, MAX	6.0, 233.8	6.0, 24.2		17.1, 474.5	6.0, 8.3	
	5%, 95%	6.0, 233.8	6.0, 23.4		28.5, 444.8	6.0, 7.8	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438669

Final Draft: 22 October 2003

Page 700 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 10 of 264)

Biomarker: NNAL (pmol/L)		Analytical Lab: Madison					
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	581.6, 405.8	31.0, 29.9		793.5, 577.7	30.0, 29.8	
	SD, SE	399.78, 94.23	12.47, 2.28		557.62, 98.57	4.45, 0.75	
	MEDIAN	609.5	28.7		720.6	28.7	
	MIN, MAX	28.7, 1591.7	28.7, 97.0		28.7, 2315.9	28.7, 45.9	
	5%, 95%	28.7, 1591.7	28.7, 28.7		54.5, 2217.4	28.7, 45.9	
	# of BLQ/ALQ Values	1/0	29/0		1/0	32/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	586.3, 426.0	41.7, 33.8		878.5, 714.7	29.3, 29.2	
	SD, SE	388.07, 94.12	43.66, 7.97		564.50, 104.82	3.63, 0.61	
	MEDIAN	643.4	28.7		768.6	28.7	
	MIN, MAX	28.7, 1390.0	28.7, 202.7		134.8, 2318.8	28.7, 50.2	
	5%, 95%	28.7, 1390.0	28.7, 194.5		218.0, 1968.9	28.7, 28.7	
	# of BLQ/ALQ Values	1/0	27/0		0/0	34/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	586.6, 443.3	36.4, 33.0		818.0, 648.1	29.7, 29.6	
	SD, SE	327.02, 77.08	22.37, 4.08		538.54, 95.20	2.81, 0.47	
	MEDIAN	649.5	28.7		726.7	28.7	
	MIN, MAX	28.7, 1117.6	28.7, 115.7		81.8, 2268.1	28.7, 39.5	
	5%, 95%	28.7, 1117.6	28.7, 111.6		136.3, 2126.2	28.7, 37.3	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438670

Final Draft: 22 October 2003

Page 701 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 11 of 264)

Biomarker: NNAL ((pg/mL)/cigarette per day)		Analytical Lab: Madison					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value*	Smokers	Non-Smokers	P-value*
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	9.1, 6.7			12.1, 9.2		
	SD, SE	7.55, 1.78			9.92, 1.75		
	MEDIAN	7.2			8.5		
	MIN, MAX	1.4, 27.8			1.9, 47.0		
	5%, 95%	1.4, 27.8			2.9, 34.8		
	# of BLQ/ALQ Values	1/0			1/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	12.1, 8.4			13.4, 10.8		
	SD, SE	13.33, 3.23			9.40, 1.75		
	MEDIAN	8.9			11.4		
	MIN, MAX	2.0, 58.2			3.8, 38.5		
	5%, 95%	2.0, 58.2			4.3, 31.2		
	# of BLQ/ALQ Values	1/0			0/0		
Overall*	N	18		NA	32		NA
	MEAN, GEO MEAN	10.4, 7.9			13.2, 10.5		
	SD, SE	9.27, 2.18			9.97, 1.76		
	MEDIAN	8.2			10.0		
	MIN, MAX	2.0, 42.4			3.7, 47.0		
	5%, 95%	2.0, 42.4			4.1, 36.7		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438671

Final Draft: 22 October 2003

Page 702 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 12 of 264)

Biomarker: NNAL ((pmol/L)/cigarette per day)		Analytical Lab: Madison					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	43.3, 32.0			57.7, 43.8		
	SD, SE	36.05, 8.50			47.46, 8.39		
	MEDIAN	34.4			40.6		
	MIN, MAX	6.5, 132.6			9.0, 224.7		
	5%, 95%	6.5, 132.6			13.6, 166.3		
	# of BLQ/ALQ Values	1/0			1/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	57.7, 40.1			64.1, 51.7		
	SD, SE	63.66, 15.44			44.91, 8.34		
	MEDIAN	42.5			54.4		
	MIN, MAX	9.6, 278.0			18.2, 183.9		
	5%, 95%	9.6, 278.0			20.6, 148.9		
	# of BLQ/ALQ Values	1/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	49.7, 37.5			62.8, 50.1		
	SD, SE	44.25, 10.43			47.64, 8.42		
	MEDIAN	39.1			47.4		
	MIN, MAX	9.6, 202.5			17.7, 224.7		
	5%, 95%	9.6, 202.5			19.4, 175.1		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 13 of 264)

Biomarker: NNAL plus NNAL-gluc (pg/24hr)		Analytical Lab: Madison					
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	17	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	803982.853, 509039.708	17773.167, 11018.595		890920.641, 630563.563	11737.457, 10761.183	
	SD, SE	609148.1353, 147740.1237	32167.6563, 5872.9837		623305.8737, 110185.9525	4713.9363, 796.8007	
	MEDIAN	529126.000	8940.000		801427.000	11100.000	
	MIN, MAX	8460.000, 2084332.500	3180.000, 181986.000		34650.000, 2307613.000	3420.000, 20100.000	
	5%, 95%	8460.000, 2084332.500	3900.000, 41624.000		37125.000, 2245880.000	4800.000, 19500.000	
	# of BLQ/ALQ Values	1/0	24/0		0/0	34/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	780888.882, 484578.381	13735.533, 11563.274		992757.038, 730891.571	14912.257, 12932.435	
	SD, SE	625370.0458, 151674.5149	10652.3865, 1944.8508		753692.7111, 139957.2229	10344.7620, 1748.5839	
	MEDIAN	540730.000	10740.000		928092.000	12180.000	
	MIN, MAX	6288.000, 2075948.000	4500.000, 61490.000		56730.000, 4046406.000	5940.000, 53066.000	
	5%, 95%	6288.000, 2075948.000	4500.000, 28208.000		97520.000, 1962480.000	6408.000, 50799.000	
	# of BLQ/ALQ Values	1/0	26/0		0/0	32/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	803959.736, 518625.587	15754.350, 11765.827		914025.181, 677520.375	13322.357, 12146.527	
	SD, SE	602618.8956, 142038.6358	17937.3794, 3274.9024		592842.6716, 104800.7683	6356.8366, 1074.5015	
	MEDIAN	619903.500	9780.000		855139.500	11790.000	
	MIN, MAX	7374.000, 2080140.250	3840.000, 97218.000		46927.500, 2468208.000	6400.000, 33874.500	
	5%, 95%	7374.000, 2080140.250	4590.000, 51557.000		66085.000, 2135046.500	6450.000, 30583.000	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438673

Final Draft: 22 October 2003

Page 704 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 14 of 264)

Biomarker: NNAL plus NNAL-gluc (pmol/24hr)		Analytical Lab: Madison					
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	17	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	3843.038, 2433.210	84.956, 52.669		4258.601, 3014.094	56.081, 51.439	
	SD, SE	2911.7280, 706.1978	153.7614, 28.0729		2979.4020, 526.6888	22.5326, 3.8087	
	MEDIAN	2529.222	42.733		3830.821	53.058	
	MIN, MAX	40.439, 9963.109	15.200, 869.893		165.627, 11030.390	16.348, 96.078	
	5%, 95%	40.439, 9963.109	18.642, 198.963		177.458, 10735.306	22.944, 93.210	
	# of BLQ/ALQ Values	1/0	24/0		0/0	34/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	3732.649, 2316.286	65.656, 55.272		4745.379, 3493.662	71.281, 61.817	
	SD, SE	2989.2688, 725.0042	50.9184, 9.2964		3602.6512, 668.9955	49.4479, 8.3582	
	MEDIAN	2584.689	51.337		4436.280	58.220	
	MIN, MAX	30.057, 9923.031	21.510, 293.922		271.169, 19341.821	28.393, 253.655	
	5%, 95%	30.057, 9923.031	21.510, 134.834		466.146, 9380.654	30.630, 242.819	
	# of BLQ/ALQ Values	1/0	26/0		0/0	32/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	3842.928, 2479.032	75.306, 56.241		4369.041, 3238.548	63.681, 58.061	
	SD, SE	2880.5182, 678.9446	85.7407, 15.6540		2833.7879, 500.9477	30.3856, 5.1361	
	MEDIAN	2963.139	46.749		4087.567	56.357	
	MIN, MAX	35.248, 9943.070	18.355, 464.702		224.314, 11798.035	30.592, 161.920	
	5%, 95%	35.248, 9943.070	21.940, 246.443		315.887, 10205.522	30.831, 146.187	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438674

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 15 of 264)

Biomarker: NNAL plus NNAL-gluc ((pg/24hr)/cigarette per day)		Analytical Lab: Madison					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value*	Smokers	Non-Smokers	P-value*
Week 1	N	17		NA	32		NA
	MEAN, GEO MEAN	54121.155, 38734.348			57697.510, 47747.375		
	SD, SE	42632.2867, 10339.8483			37505.6610, 6630.1268		
	MEDIAN	35036.000			50712.529		
	MIN, MAX	2820.000, 171072.000			8662.500, 176718.500		
	5%, 95%	2820.000, 171072.000			15822.400, 153840.867		
Week 3	# of BLQ/ALQ Values	1/0			0/0		
	N	17		NA	29		NA
	MEAN, GEO MEAN	60028.332, 45578.426			64148.130, 52875.770		
	SD, SE	36477.1862, 8847.0172			43424.9009, 8063.8017		
	MEDIAN	57631.857			49703.125		
	MIN, MAX	2096.000, 138353.600			14182.500, 192686.000		
Overall*	5%, 95%	2096.000, 138353.600			18154.500, 172716.667		
	# of BLQ/ALQ Values	1/0			0/0		
	N	18		NA	32		NA
	MEAN, GEO MEAN	57103.365, 44343.694			61047.286, 52314.024		
	SD, SE	35431.8491, 8351.3669			33743.8833, 5965.1322		
	MEDIAN	52277.687			51637.690		
Overall*	MIN, MAX	2458.000, 154712.800			16372.500, 142336.434		
	5%, 95%	2458.000, 154712.800			16521.250, 132624.738		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 16 of 264)

Biomarker: NNAL plus NNAL-gluc ((pmol/24hr)/cigarette per day)		Analytical Lab: Madison					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	17		NA	32		NA
	MEAN, GEO MEAN	258.699, 185.151			275.794, 228.233		
	SD, SE	203.7822, 49.4245			179.2769, 31.6920		
	MEDIAN	167.472			242.406		
	MIN, MAX	13.480, 817.724			41.407, 844.714		
	5%, 95%	13.480, 817.724			75.631, 735.359		
	# of BLQ/ALQ Values	1/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	286.935, 217.865			306.628, 252.746		
	SD, SE	174.3609, 42.2887			207.5710, 38.5450		
	MEDIAN	275.480			237.581		
	MIN, MAX	10.019, 661.330			67.792, 921.039		
	5%, 95%	10.019, 661.330			86.779, 825.586		
	# of BLQ/ALQ Values	1/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	272.954, 211.964			291.806, 250.061		
	SD, SE	169.3642, 39.9195			161.2956, 28.5133		
	MEDIAN	249.888			246.829		
	MIN, MAX	11.750, 739.527			78.261, 680.368		
	5%, 95%	11.750, 739.527			78.972, 633.946		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438676

Final Draft: 22 October 2003

Page 707 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 17 of 264)

Biomarker: NNAL plus NNAL-gluc (pg/mg Creatinine)		Analytical Lab: Madison					
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	17	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	632.351, 388.963	11.176, 6.201		794.208, 549.931	10.028, 9.133	
	SD, SE	604.3903, 146.5862	23.9321, 4.3694		576.5665, 101.9235	4.0580, 0.6859	
	MEDIAN	339.746	5.013		629.249	9.509	
	MIN, MAX	7.958, 2575.145	1.932, 134.956		18.519, 2476.718	2.285, 18.634	
	5%, 95%	7.958, 2575.145	2.103, 25.707		30.892, 2010.238	3.883, 17.699	
	# of BLQ/ALQ Values	1/0	24/0		0/0	34/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	533.334, 349.698	7.775, 6.330		832.490, 623.362	13.535, 11.212	
	SD, SE	387.2534, 93.9228	6.1746, 1.1273		567.0182, 105.2926	10.2695, 1.7359	
	MEDIAN	381.623	6.049		634.698	10.657	
	MIN, MAX	5.525, 1261.017	2.158, 34.375		56.481, 2275.640	3.259, 53.767	
	5%, 95%	5.525, 1261.017	2.413, 15.074		65.031, 2024.775	3.795, 41.549	
	# of BLQ/ALQ Values	1/0	26/0		0/0	32/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	581.550, 377.045	9.476, 6.637		808.453, 587.104	11.781, 10.488	
	SD, SE	470.7092, 110.9472	12.6956, 2.3179		554.2552, 97.9794	6.1400, 1.0378	
	MEDIAN	389.237	5.327		654.457	10.520	
	MIN, MAX	6.742, 1877.496	2.131, 70.371		41.775, 2250.747	3.634, 30.459	
	5%, 95%	6.742, 1877.496	2.364, 30.041		43.687, 2007.510	4.739, 27.562	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438677

Final Draft: 22 October 2003

Page 708 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 18 of 264)

Biomarker: NNAL plus NNAL-gluc (pmol/mg Creatinine) Analytical Lab: Madison

Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	17	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	3.023, 1.859	0.053, 0.030		3.796, 2.629	0.048, 0.044	
	SD, SE	2.8890, 0.7007	0.1144, 0.0209		2.7560, 0.4872	0.0194, 0.0033	
	MEDIAN	1.624	0.024		3.008	0.045	
	MIN, MAX	0.038, 12.309	0.009, 0.645		0.089, 11.839	0.011, 0.089	
	5%, 95%	0.038, 12.309	0.010, 0.123		0.148, 9.609	0.019, 0.085	
	# of BLQ/ALQ Values	1/0	24/0		0/0	34/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	2.549, 1.670	0.037, 0.030		3.979, 2.980	0.065, 0.054	
	SD, SE	1.8512, 0.4490	0.0295, 0.0054		2.7104, 0.5033	0.0491, 0.0083	
	MEDIAN	1.824	0.029		3.034	0.051	
	MIN, MAX	0.026, 6.028	0.010, 0.164		0.270, 10.878	0.016, 0.257	
	5%, 95%	0.026, 6.028	0.012, 0.072		0.311, 9.678	0.018, 0.199	
	# of BLQ/ALQ Values	1/0	26/0		0/0	32/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	2.780, 1.802	0.046, 0.032		3.865, 2.807	0.057, 0.050	
	SD, SE	2.2501, 0.5304	0.0608, 0.0111		2.6493, 0.4683	0.0293, 0.0049	
	MEDIAN	1.861	0.026		3.129	0.051	
	MIN, MAX	0.032, 8.975	0.010, 0.337		0.200, 10.759	0.018, 0.146	
	5%, 95%	0.032, 8.975	0.011, 0.144		0.209, 9.596	0.023, 0.132	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438678

Final Draft: 22 October 2003

Page 709 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2 2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 19 of 264)

Biomarker: NNAL plus NNAL-gluc ((pg/mg Creatinine)/cigarette per day) Analytical Lab: Madison

Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	17		NA	32		NA
	MEAN, GEO MEAN	60.839, 29.598			50.350, 41.642		
	SD, SE	118.7808, 28.8086			31.1852, 5.5128		
	MEDIAN	29.102			41.206		
	MIN, MAX	2.653, 515.029			4.630, 134.016		
	5%, 95%	2.653, 515.029			15.446, 116.939		
	# of BLQ/ALQ Values	1/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	48.034, 32.892			55.315, 45.097		
	SD, SE	51.9735, 12.6054			39.5695, 7.3479		
	MEDIAN	34.062			45.436		
	MIN, MAX	1.842, 235.969			14.120, 164.956		
	5%, 95%	1.842, 235.969			16.258, 155.193		
	# of BLQ/ALQ Values	1/0			0/0		
Overall†	N	18		NA	32		NA
	MEAN, GEO MEAN	53.182, 32.225			53.855, 45.461		
	SD, SE	82.3686, 19.4145			32.3057, 5.7109		
	MEDIAN	29.297			43.072		
	MIN, MAX	2.248, 375.499			10.444, 133.834		
	5%, 95%	2.248, 375.499			14.783, 131.185		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

† Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234) will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438679

Final Draft: 22 October 2003

Page 710 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 20 of 264)

Biomarker: NNAL plus NNAL-gluc (pmol/mg Creatinine)/cigarette per day		Analytical Lab: Madison					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value*	Smokers	Non-Smokers	P-value*
Week 1	N	17		NA	32		NA
	MEAN, GEO MEAN	0.291, 0.142			0.241, 0.199		
	SD, SE	0.5678, 0.1377			0.1490, 0.0263		
	MEDIAN	0.139			0.198		
	MIN, MAX	0.013, 2.462			0.022, 0.641		
	5%, 95%	0.013, 2.462			0.074, 0.559		
	# of BLQ/ALQ Values	1/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	0.230, 0.157			0.265, 0.216		
	SD, SE	0.2484, 0.0603			0.1891, 0.0351		
	MEDIAN	0.163			0.217		
	MIN, MAX	0.009, 1.128			0.068, 0.789		
	5%, 95%	0.009, 1.128			0.078, 0.742		
	# of BLQ/ALQ Values	1/0			0/0		
Overall*	N	18		NA	32		NA
	MEAN, GEO MEAN	0.255, 0.155			0.258, 0.218		
	SD, SE	0.3937, 0.0928			0.1543, 0.0273		
	MEDIAN	0.140			0.206		
	MIN, MAX	0.011, 1.795			0.050, 0.640		
	5%, 95%	0.011, 1.795			0.071, 0.627		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics).

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438680

Final Draft: 22 October 2003

Page 711 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 21 of 264)

Biomarker: NNAL plus NNAL-gluc (pg/mL)		Analytical Lab: Madison					
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	17	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	532.4, 308.3	13.7, 7.5		554.4, 360.2	6.0, 6.0	
	SD, SE	500.33, 121.35	33.35, 6.09		459.48, 81.23	0.17, 0.03	
	MEDIAN	445.5	6.0		484.0	6.0	
	MIN, MAX	6.0, 1773.9	6.0, 185.7		13.5, 2045.7	6.0, 7.0	
	5%, 95%	6.0, 1773.9	6.0, 47.3		16.5, 1604.2	6.0, 6.0	
	# of BLQ/ALQ Values	1/0	24/0		0/0	34/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	427.5, 286.6	7.5, 6.6		626.3, 425.9	7.2, 6.6	
	SD, SE	313.45, 76.02	7.53, 1.38		557.17, 103.46	4.74, 0.80	
	MEDIAN	415.9	6.0		482.0	6.0	
	MIN, MAX	6.0, 1235.3	6.0, 47.3		30.5, 2223.3	6.0, 31.4	
	5%, 95%	6.0, 1235.3	6.0, 8.6		53.0, 1842.9	6.0, 17.7	
	# of BLQ/ALQ Values	1/0	26/0		0/0	32/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	486.9, 321.5	10.6, 7.3		573.7, 393.7	6.6, 6.4	
	SD, SE	362.20, 85.37	17.77, 3.24		462.07, 81.68	2.37, 0.40	
	MEDIAN	385.6	6.0		453.3	6.0	
	MIN, MAX	6.0, 1230.7	6.0, 95.9		22.0, 1663.1	6.0, 18.7	
	5%, 95%	6.0, 1230.7	6.0, 47.3		34.8, 1653.7	6.0, 11.9	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438681

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 22 of 264)

Biomarker: NNAL plus NNAL-gluc (pmol/L)		Analytical Lab: Madison					
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	17	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	2544.7, 1473.7	65.3, 35.9		2650.1, 1721.5	28.8, 28.8	
	SD, SE	2391.57, 580.04	159.42, 29.11		2196.31, 388.26	0.81, 0.14	
	MEDIAN	2129.5	28.7		2313.3	28.7	
	MIN, MAX	28.7, 8479.2	28.7, 887.6		64.5, 9778.4	28.7, 33.5	
	5%, 95%	28.7, 8479.2	28.7, 226.1		78.9, 7668.1	28.7, 28.7	
	# of BLQ/ALQ Values	1/0	24/0		0/0	34/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	2043.4, 1370.0	36.1, 31.5		2993.7, 2035.8	34.6, 31.6	
	SD, SE	1498.29, 363.39	36.01, 6.57		2663.28, 494.56	22.66, 3.83	
	MEDIAN	1988.0	28.7		2304.0	28.7	
	MIN, MAX	28.7, 5904.7	28.7, 226.1		145.8, 10627.4	28.7, 150.1	
	5%, 95%	28.7, 5904.7	28.7, 41.1		253.3, 8809.1	28.7, 84.6	
	# of BLQ/ALQ Values	1/0	26/0		0/0	32/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	2327.4, 1536.6	50.7, 34.9		2742.2, 1881.7	31.7, 30.6	
	SD, SE	1731.30, 408.07	84.92, 15.50		2208.67, 390.44	11.32, 1.91	
	MEDIAN	1843.1	28.7		2166.6	28.7	
	MIN, MAX	28.7, 5882.5	28.7, 458.2		105.2, 7949.4	28.7, 89.4	
	5%, 95%	28.7, 5882.5	28.7, 226.1		166.1, 7904.4	28.7, 56.7	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438682

Final Draft: 22 October 2003

Page 713 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 23 of 264)

Biomarker: NNAL plus NNAL-gluc ((pg/mL)/cigarette per day)		Analytical Lab: Madison					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	17		NA	32		NA
	MEAN, GEO MEAN	35.9, 23.5			36.1, 27.3		
	SD, SE	33.16, 8.04			27.44, 4.85		
	MEDIAN	27.3			26.7		
	MIN, MAX	2.0, 128.6			4.1, 109.3		
	5%, 95%	2.0, 128.6			6.8, 95.6		
	# of BLQ/ALQ Values	1/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	43.2, 27.0			41.2, 30.8		
	SD, SE	56.18, 13.62			31.58, 5.86		
	MEDIAN	25.2			23.7		
	MIN, MAX	2.0, 247.1			7.6, 105.9		
	5%, 95%	2.0, 247.1			10.0, 100.6		
	# of BLQ/ALQ Values	1/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	39.2, 27.3			39.2, 30.4		
	SD, SE	37.94, 8.94			28.33, 5.01		
	MEDIAN	31.4			26.1		
	MIN, MAX	2.0, 168.1			7.2, 109.3		
	5%, 95%	2.0, 168.1			8.7, 98.1		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438683

Final Draft: 22 October 2003

Page 714 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 24 of 264)

Biomarker: NNAL plus NNAL-gluc ((pmol/L)/cigarette per day)		Analytical Lab: Madison					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value*	Smokers	Non-Smokers	P-value*
Week 1	N	17		NA	32		NA
	MEAN, GEO MEAN	171.7, 112.2			172.4, 130.4		
	SD, SE	158.49, 38.44			131.15, 23.18		
	MEDIAN	130.7			127.8		
	MIN, MAX	9.6, 614.6			19.7, 522.5		
	5%, 95%	9.6, 614.6			32.3, 456.7		
Week 3	# of BLQ/ALQ Values	1/0			0/0		
	N	17		NA	29		NA
	MEAN, GEO MEAN	206.4, 128.9			196.8, 147.3		
	SD, SE	268.48, 65.12			151.02, 28.04		
	MEDIAN	120.5			113.4		
	MIN, MAX	9.6, 1180.9			36.5, 506.1		
Overall*	5%, 95%	9.6, 1180.9			47.7, 481.1		
	# of BLQ/ALQ Values	1/0			0/0		
	N	18		NA	32		NA
	MEAN, GEO MEAN	187.5, 130.6			187.3, 145.1		
	SD, SE	181.30, 42.73			135.44, 23.94		
	MEDIAN	149.8			124.8		
	MIN, MAX	9.6, 803.4			34.4, 522.5		
	5%, 95%	9.6, 803.4			41.5, 468.9		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 25 of 264)

Biomarker: NNAL-O-glucuronide (pmol/L)		Analytical Lab: Madison					
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	17	29	<.0001	32	32	<.0001
	MEAN, GEO MEAN	1950.1, NA	37.9, NA		1856.6, 1069.4	0.2, NA	
	SD, SE	2050.37, 497.29	162.11, 30.10		1691.41, 299.00	0.85, 0.15	
	MEDIAN	1543.0	0.0		1631.9	0.0	
	MIN, MAX	0.0, 7358.3	0.0, 859.0		24.4, 7462.5	0.0, 4.8	
	5%, 95%	0.0, 7358.3	0.0, 197.4		35.9, 5458.8	0.0, 0.0	
	# of BLQ/ALQ Values	1/0	29/0		1/0	32/0	
Week 3	N	17	28	<.0001	29	35	<.0001
	MEAN, GEO MEAN	1457.1, NA	2.0, NA		2115.3, 1152.9	5.3, NA	
	SD, SE	1136.78, 275.71	6.52, 1.23		2223.97, 412.98	19.50, 3.30	
	MEDIAN	1234.2	0.0		1443.6	0.0	
	MIN, MAX	0.0, 4514.7	0.0, 31.5		11.0, 9536.6	0.0, 99.9	
	5%, 95%	0.0, 4514.7	0.0, 12.4		35.4, 7004.1	0.0, 55.9	
	# of BLQ/ALQ Values	1/0	27/0		0/0	34/0	
Overall†	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	1744.6, NA	19.2, NA		1924.2, 1135.3	2.7, NA	
	SD, SE	1455.58, 343.08	80.23, 14.65		1730.55, 305.92	9.75, 1.65	
	MEDIAN	1277.7	0.0		1626.1	0.0	
	MIN, MAX	0.0, 4879.9	0.0, 429.5		23.5, 5778.3	0.0, 50.0	
	5%, 95%	0.0, 4879.9	0.0, 114.5		29.9, 5681.3	0.0, 28.0	

* P-value from Wilcoxon rank-sum test.

† Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 26 of 264)

Biomarker: NNAL-O-glucuronide ((pmol/L)/cigarette per day) Analytical Lab: Madison

Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	17		NA	32		NA
	MEAN, GEO MEAN	128.9, NA			114.7, 81.0		
	SD, SE	125.32, 30.39			92.49, 16.35		
	MEDIAN	85.7			86.2		
	MIN, MAX	0.0, 481.9			6.1, 363.9		
	5%, 95%	0.0, 481.9			16.9, 339.2		
	# of BLQ/ALQ Values	1/0			1/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	148.7, NA			132.7, 83.5		
	SD, SE	206.23, 50.02			117.49, 21.82		
	MEDIAN	80.1			77.7		
	MIN, MAX	0.0, 902.9			2.8, 454.1		
	5%, 95%	0.0, 902.9			8.9, 350.2		
	# of BLQ/ALQ Values	1/0			0/0		
Overall†	N	18		NA	32		NA
	MEAN, GEO MEAN	138.3, NA			124.6, 88.0		
	SD, SE	139.15, 32.80			96.22, 17.01		
	MEDIAN	107.8			86.6		
	MIN, MAX	0.0, 601.0			7.5, 356.9		
	5%, 95%	0.0, 601.0			10.4, 306.1		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

† Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438686

Final Draft: 22 October 2003

Page 717 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 27 of 264)

Biomarker: NNAL-O-glucuronide (pmol/24hr)		Analytical Lab. Madison					
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	17	29	<.0001	32	32	<.0001
	MEAN, GEO MEAN	2904.964, NA	38.243, NA		2911.039, 1872.337	0.147, NA	
	SD, SE	2489.6679, 603.8332	158.0832, 29.3553		2191.8620, 387.4701	0.8316, 0.1470	
	MEDIAN	1833.188	0.000		2516.876	0.000	
	MIN, MAX	0.000, 8646.003	0.000, 841.820		51.240, 8788.668	0.000, 4.704	
	5%, 95%	0.000, 8646.003	0.000, 173.712		98.725, 7630.840	0.000, 0.000	
	# of BLQ/ALQ Values	1/0	29/0		1/0	32/0	
Week 3	N	17	28	<.0001	29	35	<.0001
	MEAN, GEO MEAN	2636.817, NA	3.352, NA		3277.052, 1978.544	10.165, NA	
	SD, SE	2140.5686, 519.1641	10.3068, 1.9478		3205.0765, 595.1678	38.8545, 6.5676	
	MEDIAN	1703.196	0.000		2646.905	0.000	
	MIN, MAX	0.000, 7252.530	0.000, 40.950		20.460, 17356.612	0.000, 168.831	
	5%, 95%	0.000, 7252.530	0.000, 36.120		65.136, 6821.100	0.000, 160.433	
	# of BLQ/ALQ Values	1/0	27/0		0/0	34/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	2839.652, NA	20.049, NA		2996.589, 1953.512	5.150, NA	
	SD, SE	2316.2775, 545.9518	78.3074, 14.2969		2267.1090, 400.7720	19.4133, 3.2815	
	MEDIAN	2120.435	0.000		2644.194	0.000	
	MIN, MAX	0.000, 7949.267	0.000, 420.910		58.188, 10073.384	0.000, 84.416	
	5%, 95%	0.000, 7949.267	0.000, 107.331		59.593, 7804.884	0.000, 80.217	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438687

Final Draft: 22 October 2003

Page 718 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 28 of 264)

Biomarker: NNAL-O-glucuronide ((pmol/24hr)/cigarette per day)		Analytical Lab: Madison					
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	17		NA	32		NA
	MEAN, GEO MEAN	191.695, NA			178.194, 141.777		
	SD, SE	154.3645, 37.4389			119.7548, 21.1699		
	MEDIAN	120.232			165.201		
	MIN, MAX	0.000, 574.157			12.810, 585.911		
	5%, 95%	0.000, 574.157			47.073, 437.301		
	# of BLQ/ALQ Values	1/0			1/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	203.742, NA			201.878, 143.136		
	SD, SE	132.0991, 32.0387			168.0591, 31.2078		
	MEDIAN	168.115			147.793		
	MIN, MAX	0.000, 505.646			5.115, 826.505		
	5%, 95%	0.000, 505.646			16.284, 517.290		
	# of BLQ/ALQ Values	1/0			0/0		
Overall*	N	18		NA	32		NA
	MEAN, GEO MEAN	198.934, NA			189.637, 151.404		
	SD, SE	129.3352, 30.4846			118.5019, 20.9484		
	MEDIAN	165.534			166.137		
	MIN, MAX	0.000, 539.902			14.547, 520.326		
	5%, 95%	0.000, 539.902			27.239, 476.665		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438688

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 29 of 264)

Biomarker: NNAL-O-glucuronide (pmol/mg Creatinine)		Analytical Lab: Madison					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	17	29	<.0001	32	32	<.0001
	MEAN, GEO MEAN	2.232, NA	0.027, NA		2.590, 1.632	0.000, NA	
	SD, SE	2.1168, 0.5134	0.1166, 0.0217		2.0000, 0.3535	0.0005, 0.0001	
	MEDIAN	1.190	0.000		2.237	0.000	
	MIN, MAX	0.000, 8.643	0.000, 0.624		0.027, 7.951	0.000, 0.003	
	5%, 95%	0.000, 8.643	0.000, 0.107		0.082, 7.656	0.000, 0.000	
	# of BLQ/ALQ Values	1/0	29/0		1/0	32/0	
Week 3	N	17	28	<.0001	29	35	<.0001
	MEAN, GEO MEAN	1.818, NA	0.002, NA		2.688, 1.686	0.009, NA	
	SD, SE	1.3733, 0.3331	0.0056, 0.0011		2.1935, 0.4073	0.0359, 0.0061	
	MEDIAN	1.355	0.000		1.939	0.000	
	MIN, MAX	0.000, 4.312	0.000, 0.023		0.020, 9.761	0.000, 0.171	
	5%, 95%	0.000, 4.312	0.000, 0.019		0.043, 6.968	0.000, 0.131	
	# of BLQ/ALQ Values	1/0	27/0		0/0	34/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	2.037, NA	0.014, NA		2.618, 1.692	0.005, NA	
	SD, SE	1.6980, 0.4002	0.0576, 0.0105		1.9471, 0.3442	0.0181, 0.0031	
	MEDIAN	1.169	0.000		2.014	0.000	
	MIN, MAX	0.000, 6.478	0.000, 0.312		0.035, 7.312	0.000, 0.086	
	5%, 95%	0.000, 6.478	0.000, 0.065		0.051, 7.084	0.000, 0.066	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438689

Final Draft: 22 October 2003

Page 720 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 30 of 264)

Biomarker: NNAL-O-glucuronide ((pmol/mg Creatinine)/cigarette per day) Analytical Lab: Madison

Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	17		NA	32		NA
	MEAN, GEO MEAN	0.211, NA			0.156, 0.124		
	SD, SE	0.3990, 0.0968			0.1057, 0.0187		
	MEDIAN	0.119			0.125		
	MIN, MAX	0.000, 1.729			0.007, 0.510		
	5%, 95%	0.000, 1.729			0.041, 0.364		
	# of BLQ/ALQ Values	1/0			1/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	0.165, NA			0.170, 0.122		
	SD, SE	0.1919, 0.0466			0.1322, 0.0245		
	MEDIAN	0.108			0.122		
	MIN, MAX	0.000, 0.862			0.005, 0.494		
	5%, 95%	0.000, 0.862			0.011, 0.465		
	# of BLQ/ALQ Values	1/0			0/0		
Overall*	N	18		NA	32		NA
	MEAN, GEO MEAN	0.184, NA			0.166, 0.132		
	SD, SE	0.2853, 0.0672			0.1068, 0.0189		
	MEDIAN	0.103			0.140		
	MIN, MAX	0.000, 1.296			0.009, 0.488		
	5%, 95%	0.000, 1.296			0.023, 0.364		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

NOTE: The NNAL and NNAL-gluc data is presented for informational purposes only. The assay used for analysis was not validated, and therefore, the data for these analytes is not valid.

PM3006438690

Final Draft: 22 October 2003

Page 721 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 31 of 264)

Biomarker: Cotinine (ug/24hr)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	1683.977, 1226.756	4.187, 2.268		1833.759, 1377.866	2.289, 1.974	
	SD, SE	920.8075, 217.0364	6.2628, 1.1434		1274.5169, 225.3049	1.3989, 0.2365	
	MEDIAN	1908.816	1.830		1583.006	1.950	
	MIN, MAX	26.790, 3201.831	0.530, 27.900		50.050, 6435.660	0.570, 6.912	
	5%, 95%	26.790, 3201.831	0.715, 20.140		308.979, 3606.938	0.800, 6.825	
	# of BLQ/ALQ Values	0/0	19/0		0/0	30/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	1784.287, 1256.439	5.196, 2.549		1837.173, 1433.924	2.387, 2.083	
	SD, SE	902.3151, 212.6777	10.7544, 1.9635		1174.1091, 210.8762	1.3526, 0.2286	
	MEDIAN	1769.274	1.917		1686.630	2.200	
	MIN, MAX	13.950, 3133.273	0.625, 59.280		148.738, 4366.890	0.660, 7.795	
	5%, 95%	13.950, 3133.273	0.815, 13.221		350.900, 4252.954	0.750, 4.875	
	# of BLQ/ALQ Values	0/0	18/0		0/0	29/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	2040.610, 1231.977	3.809, 2.464		1902.946, 1558.715	2.248, 2.050	
	SD, SE	1576.7984, 382.4298	5.2300, 0.9549		1132.3107, 210.2648	1.0814, 0.1828	
	MEDIAN	1600.536	2.032		1655.220	2.050	
	MIN, MAX	6.393, 5162.740	0.750, 25.870		225.246, 4886.167	0.940, 6.420	
	5%, 95%	6.393, 5162.740	1.072, 15.370		391.688, 3866.576	0.990, 4.740	
	# of BLQ/ALQ Values	0/0	18/0		0/0	32/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	1830.019, 1303.963	4.397, 2.599		1818.890, 1460.495	2.308, 2.091	
	SD, SE	1019.6382, 240.3310	6.2744, 1.1455		1095.3362, 193.6299	1.0681, 0.1805	
	MEDIAN	1786.237	1.991		1681.960	2.150	
	MIN, MAX	15.711, 3774.690	0.787, 30.043		141.345, 4483.278	0.967, 5.145	
	5%, 95%	15.711, 3774.690	1.092, 16.027		374.266, 3982.288	0.980, 4.770	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics).

PM3006438691

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 32 of 264)

Biomarker: Cotinine (nmol/24hr)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	9556.568, 6961.841	23.762, 12.871		10406.583, 7819.392	12.989, 11.201	
	SD, SE	5225.5828, 1231.6817	35.5415, 6.4890		7232.8836, 1278.6053	7.9390, 1.3419	
	MEDIAN	10832.531	10.383		8983.556	11.066	
	MIN, MAX	152.033, 18170.391	3.008, 158.333		284.034, 36522.371	3.235, 39.226	
	5%, 95%	152.033, 18170.391	4.058, 114.295		1753.456, 20469.373	4.540, 38.732	
	# of BLQ/ALQ Values	0/0	19/0		0/0	30/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	10125.830, 7130.292	29.490, 14.465		10425.957, 8137.517	13.549, 11.824	
	SD, SE	5120.6381, 1206.9460	61.0312, 11.1427		6663.0694, 1196.7226	7.6759, 1.2975	
	MEDIAN	10040.630	10.879		9571.625	12.485	
	MIN, MAX	79.166, 17781.324	3.547, 336.414		844.088, 24782.101	3.746, 44.237	
	5%, 95%	79.166, 17781.324	4.625, 75.029		1991.358, 24135.514	4.256, 27.666	
	# of BLQ/ALQ Values	0/0	18/0		0/0	29/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	11580.459, 6991.468	21.615, 13.985		10799.218, 8845.710	12.756, 11.636	
	SD, SE	8948.3309, 2170.2890	29.6804, 5.4189		6425.8632, 1193.2528	6.1368, 1.0373	
	MEDIAN	9083.042	11.532		9393.374	11.634	
	MIN, MAX	36.280, 29298.550	4.256, 146.812		1278.271, 27728.998	5.335, 36.434	
	5%, 95%	36.280, 29298.550	6.084, 87.225		2222.829, 21942.819	5.618, 26.900	
	# of BLQ/ALQ Values	0/0	18/0		0/0	32/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	10385.356, 7399.989	24.956, 14.747		10322.202, 8288.311	13.098, 11.867	
	SD, SE	5786.4474, 1363.8787	35.6075, 6.5010		6216.0336, 1098.8499	6.0612, 1.0245	
	MEDIAN	10136.892	11.298		9545.122	12.201	
	MIN, MAX	89.160, 21421.368	4.464, 170.496		802.131, 25442.605	5.486, 29.198	
	5%, 95%	89.160, 21421.368	6.195, 90.955		2123.957, 22599.486	5.562, 27.068	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438692

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 33 of 264)

Biomarker: Cotinine ((μ g/24hr)/cigarette per day) Analytical Lab: Harrogate		Male			Female		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*	Smokers	Non-Smokers	P-value*
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	125.049, 96.672			134.159, 104.334		
	SD, SE	89.1273, 21.0075			118.9202, 21.0223		
	MEDIAN	101.557			98.981		
	MIN, MAX	8.930, 385.805			25.025, 643.566		
	5%, 95%	8.930, 385.805			29.911, 304.113		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	173.708, 99.521			145.277, 116.936		
	SD, SE	287.4993, 67.7642			105.1783, 18.8906		
	MEDIAN	117.995			107.678		
	MIN, MAX	4.650, 1308.045			32.188, 485.210		
	5%, 95%	4.650, 1308.045			41.747, 342.365		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	155.573, 115.877			135.216, 112.764		
	SD, SE	81.4576, 19.7564			89.9849, 16.7098		
	MEDIAN	160.120			111.844		
	MIN, MAX	2.131, 320.107			45.833, 335.938		
	5%, 95%	2.131, 320.107			46.306, 330.911		
	# of BLQ/ALQ Values	0/0			0/0		
Overall*	N	18		NA	32		NA
	MEAN, GEO MEAN	150.028, 108.591			137.396, 115.621		
	SD, SE	140.5316, 33.1236			94.0927, 16.6334		
	MEDIAN	118.237			102.109		
	MIN, MAX	5.237, 671.319			47.120, 486.562		
	5%, 95%	5.237, 671.319			48.557, 299.233		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438693

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 34 of 264)

Biomarker: Cotinine (nmol/24hr)/cigarette per day		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	709.652, 548.614			761.351, 592.098		
	SD, SE	505.7971, 119.2175			674.8723, 119.3017		
	MEDIAN	576.335			561.716		
	MIN, MAX	50.678, 2189.442			142.017, 3652.237		
	5%, 95%	50.678, 2189.442			169.746, 1725.843		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	985.790, 564.781			824.446, 663.612		
	SD, SE	1631.5586, 384.5620			596.8868, 107.2040		
	MEDIAN	669.619			611.073		
	MIN, MAX	26.389, 7423.156			182.668, 2753.567		
	5%, 95%	26.389, 7423.156			236.913, 1942.924		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	882.879, 657.602			767.351, 639.936		
	SD, SE	462.2721, 112.1175			510.6639, 94.8279		
	MEDIAN	908.683			634.712		
	MIN, MAX	12.093, 1816.608			260.099, 1906.445		
	5%, 95%	12.093, 1816.608			262.788, 1877.918		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	851.411, 616.255			779.721, 656.148		
	SD, SE	797.5169, 187.9765			533.9762, 94.3945		
	MEDIAN	670.996			579.469		
	MIN, MAX	29.720, 3809.735			267.406, 2761.241		
	5%, 95%	29.720, 3809.735			275.561, 1698.146		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438694

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 35 of 264)

Biomarker: Cotinine (µg/mg Creatinine)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value*	Smokers	Non-Smokers	P-value*
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	1.448, 0.928	0.003, NA		1.697, 1.202	0.002, NA	
	SD, SE	1.3218, 0.3115	0.0041, 0.0008		1.1734, 0.2074	0.0017, 0.0003	
	MEDIAN	1.260	0.001		1.628	0.002	
	MIN, MAX	0.025, 5.808	0.000, 0.020		0.042, 4.207	0.000, 0.010	
	5%, 95%	0.025, 5.808	0.000, 0.010		0.203, 3.903	0.001, 0.005	
	# of BLQ/ALQ Values	0/0	19/0		0/0	30/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	1.431, 0.925	0.004, NA		1.499, 1.139	0.002, NA	
	SD, SE	1.1733, 0.2765	0.0102, 0.0019		1.0524, 0.1890	0.0014, 0.0002	
	MEDIAN	1.264	0.001		1.250	0.002	
	MIN, MAX	0.016, 5.177	0.000, 0.057		0.148, 4.123	0.000, 0.007	
	5%, 95%	0.016, 5.177	0.000, 0.007		0.275, 3.337	0.001, 0.005	
	# of BLQ/ALQ Values	0/0	18/0		0/0	29/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	1.378, 0.893	0.002, NA		1.745, 1.329	0.002, 0.002	
	SD, SE	0.9164, 0.2223	0.0028, 0.0005		1.3149, 0.2442	0.0015, 0.0003	
	MEDIAN	1.292	0.001		1.410	0.002	
	MIN, MAX	0.006, 3.315	0.000, 0.014		0.224, 5.186	0.001, 0.009	
	5%, 95%	0.006, 3.315	0.000, 0.009		0.383, 4.641	0.001, 0.005	
	# of BLQ/ALQ Values	0/0	18/0		0/0	32/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	1.412, 0.957	0.003, NA		1.666, 1.253	0.002, NA	
	SD, SE	1.0606, 0.2500	0.0049, 0.0009		1.1632, 0.2056	0.0013, 0.0002	
	MEDIAN	1.295	0.001		1.349	0.002	
	MIN, MAX	0.016, 4.572	0.000, 0.026		0.138, 4.505	0.000, 0.006	
	5%, 95%	0.016, 4.572	0.001, 0.009		0.266, 3.886	0.001, 0.006	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics).

PM3006438695

Final Draft: 22 October 2003

Page 726 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 36 of 264)

Biomarker: Cotinine (nmol/mg Creatinine)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	8.216, 5.264	0.015, NA		9.630, 6.822	0.012, NA	
	SD, SE	7.5011, 1.7680	0.0234, 0.0043		6.6590, 1.1772	0.0094, 0.0016	
	MEDIAN	7.151	0.006		9.239	0.011	
	MIN, MAX	0.142, 32.960	0.000, 0.114		0.238, 23.875	0.000, 0.057	
	5%, 95%	0.142, 32.960	0.000, 0.057		1.132, 22.150	0.006, 0.028	
	# of BLQ/ALQ Values	0/0	19/0		0/0	30/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	8.122, 5.249	0.022, NA		8.506, 6.461	0.012, NA	
	SD, SE	6.6582, 1.5693	0.0577, 0.0105		5.9724, 1.0727	0.0080, 0.0013	
	MEDIAN	7.174	0.006		7.094	0.011	
	MIN, MAX	0.091, 29.379	0.000, 0.323		0.840, 23.398	0.000, 0.040	
	5%, 95%	0.091, 29.379	0.000, 0.040		1.561, 18.937	0.006, 0.028	
	# of BLQ/ALQ Values	0/0	18/0		0/0	29/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	7.819, 5.065	0.012, NA		9.903, 7.544	0.012, 0.010	
	SD, SE	5.2007, 1.2614	0.0158, 0.0029		7.4619, 1.3856	0.0087, 0.0015	
	MEDIAN	7.332	0.006		8.002	0.011	
	MIN, MAX	0.034, 18.813	0.000, 0.079		1.271, 29.431	0.006, 0.051	
	5%, 95%	0.034, 18.813	0.000, 0.051		2.174, 26.338	0.006, 0.028	
	# of BLQ/ALQ Values	0/0	18/0		0/0	32/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	8.016, 5.428	0.017, NA		9.455, 7.113	0.012, 0.010	
	SD, SE	6.0188, 1.4186	0.0278, 0.0051		6.6015, 1.1670	0.0073, 0.0012	
	MEDIAN	7.346	0.008		7.653	0.009	
	MIN, MAX	0.089, 25.944	0.000, 0.149		0.783, 25.568	0.002, 0.036	
	5%, 95%	0.089, 25.944	0.004, 0.051		1.510, 22.053	0.006, 0.032	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438696

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 37 of 264)

Biomarker: Cotinine ((µg/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	0.145, 0.073			0.120, 0.091		
	SD, SE	0.2624, 0.0618			0.0945, 0.0167		
	MEDIAN	0.073			0.098		
	MIN, MAX	0.008, 1.162			0.021, 0.390		
	5%, 95%	0.008, 1.162			0.026, 0.366		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	0.216, 0.073			0.118, 0.093		
	SD, SE	0.5939, 0.1400			0.0803, 0.0144		
	MEDIAN	0.070			0.095		
	MIN, MAX	0.005, 2.589			0.023, 0.336		
	5%, 95%	0.005, 2.589			0.025, 0.303		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	0.121, 0.084			0.127, 0.096		
	SD, SE	0.1159, 0.0281			0.1158, 0.0215		
	MEDIAN	0.106			0.096		
	MIN, MAX	0.002, 0.546			0.031, 0.580		
	5%, 95%	0.002, 0.546			0.035, 0.321		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	0.159, 0.080			0.124, 0.099		
	SD, SE	0.3206, 0.0756			0.0900, 0.0159		
	MEDIAN	0.087			0.105		
	MIN, MAX	0.005, 1.432			0.034, 0.435		
	5%, 95%	0.005, 1.432			0.035, 0.311		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438697

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 38 of 264)

Biomarker: Cotinine (nmol/mg Creatinine)/cigarette per day Analytical Lab: Harrogate

Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	0.825, 0.415			0.679, 0.517		
	SD, SE	1.4884, 0.3508			0.5367, 0.0949		
	MEDIAN	0.411			0.554		
	MIN, MAX	0.047, 6.592			0.119, 2.215		
	5%, 95%	0.047, 6.592			0.149, 2.078		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	1.223, 0.416			0.667, 0.527		
	SD, SE	3.3696, 0.7942			0.4562, 0.0819		
	MEDIAN	0.398			0.540		
	MIN, MAX	0.030, 14.690			0.129, 1.909		
	5%, 95%	0.030, 14.690			0.142, 1.721		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	0.688, 0.476			0.722, 0.546		
	SD, SE	0.6579, 0.1596			0.6568, 0.1220		
	MEDIAN	0.599			0.544		
	MIN, MAX	0.011, 3.099			0.177, 3.292		
	5%, 95%	0.011, 3.099			0.201, 1.821		
	# of BLQ/ALQ Values	0/0			0/0		
Overall*	N	18		NA	32		NA
	MEAN, GEO MEAN	0.904, 0.454			0.703, 0.563		
	SD, SE	1.8194, 0.4288			0.5114, 0.0904		
	MEDIAN	0.493			0.593		
	MIN, MAX	0.029, 8.127			0.190, 2.472		
	5%, 95%	0.029, 8.127			0.199, 1.767		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438698

Final Draft: 22 October 2003

Page 729 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 39 of 264)

Biomarker: Cotinine (ng/mL)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	1001.8, 749.5	2.3, 1.5		1044.9, 787.0	1.2, 1.1	
	SD, SE	574.80, 135.48	2.91, 0.53		650.99, 115.08	0.69, 0.12	
	MEDIAN	925.7	1.0		911.1	1.0	
	MIN, MAX	19.0, 2263.4	1.0, 14.1		18.2, 2626.8	1.0, 4.8	
	5%, 95%	19.0, 2263.4	1.0, 10.0		226.0, 2534.2	1.0, 2.2	
	# of BLQ/ALQ Values	0/0	19/0		0/0	30/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	1183.3, 887.6	2.7, 1.6		1138.3, 880.3	1.2, 1.1	
	SD, SE	626.79, 147.74	4.14, 0.76		877.59, 157.62	0.40, 0.07	
	MEDIAN	1065.2	1.0		975.4	1.0	
	MIN, MAX	15.5, 2343.3	1.0, 20.8		81.5, 4778.6	1.0, 2.5	
	5%, 95%	15.5, 2343.3	1.0, 11.7		221.4, 2646.6	1.0, 2.4	
	# of BLQ/ALQ Values	0/0	18/0		0/0	29/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	1107.1, 728.7	2.1, 1.4		1068.7, 908.3	1.1, 1.0	
	SD, SE	744.03, 180.45	3.49, 0.64		570.14, 105.87	0.46, 0.08	
	MEDIAN	844.3	1.0		1005.9	1.0	
	MIN, MAX	6.1, 2858.1	1.0, 19.9		121.1, 2580.2	1.0, 3.7	
	5%, 95%	6.1, 2858.1	1.0, 5.3		311.8, 2101.4	1.0, 1.2	
	# of BLQ/ALQ Values	0/0	18/0		0/0	32/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	1101.6, 829.0	2.3, 1.6		1062.8, 856.8	1.1, 1.1	
	SD, SE	549.70, 129.57	2.96, 0.54		659.30, 116.55	0.42, 0.07	
	MEDIAN	1065.0	1.1		914.3	1.0	
	MIN, MAX	13.5, 1962.5	1.0, 13.9		73.6, 3090.2	1.0, 2.8	
	5%, 95%	13.5, 1962.5	1.0, 10.6		275.9, 2617.9	1.0, 2.7	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438699

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 40 of 264)

Biomarker: Cotinine (nmol/L)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	5685.4, 4253.4	12.8, 8.8		5930.1, 4466.2	6.8, 6.3	
	SD, SE	3262.01, 768.86	16.53, 3.02		3694.37, 653.08	3.89, 0.66	
	MEDIAN	5253.1	5.7		5170.2	5.7	
	MIN, MAX	107.8, 12844.8	5.7, 80.0		103.3, 14907.1	5.7, 27.2	
	5%, 95%	107.8, 12844.8	5.7, 56.8		1282.6, 14381.6	5.7, 12.5	
	# of BLQ/ALQ Values	0/0	19/0		0/0	30/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	6715.1, 5037.2	15.3, 9.3		6459.7, 4995.6	6.6, 6.4	
	SD, SE	3557.04, 838.40	23.49, 4.29		4980.33, 894.49	2.24, 0.38	
	MEDIAN	6045.1	5.7		5535.4	5.7	
	MIN, MAX	88.0, 13298.2	5.7, 118.0		462.5, 27118.6	5.7, 14.2	
	5%, 95%	88.0, 13298.2	5.7, 66.4		1256.4, 15019.5	5.7, 13.6	
	# of BLQ/ALQ Values	0/0	18/0		0/0	29/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	6282.8, 4135.0	11.7, 8.0		6064.6, 5154.5	6.2, 6.0	
	SD, SE	4222.34, 1024.07	19.79, 3.61		3235.56, 600.83	2.59, 0.44	
	MEDIAN	4791.4	5.7		5708.5	5.7	
	MIN, MAX	34.6, 16219.7	5.7, 112.9		687.2, 14642.6	5.7, 21.0	
	5%, 95%	34.6, 16219.7	5.7, 30.1		1769.5, 11925.4	5.7, 6.8	
	# of BLQ/ALQ Values	0/0	18/0		0/0	32/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	6251.7, 4705.3	13.3, 9.2		6031.5, 4862.6	6.5, 6.3	
	SD, SE	3119.51, 735.28	16.80, 3.07		3741.56, 661.42	2.38, 0.40	
	MEDIAN	6043.6	6.4		5188.9	5.7	
	MIN, MAX	76.8, 11137.0	5.7, 78.7		417.7, 17537.1	5.7, 15.9	
	5%, 95%	76.8, 11137.0	5.7, 60.2		1566.0, 14856.4	5.7, 15.5	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438700

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 41 of 264)

Biomarker: Cotinine ((ng/mL)/cigarette per day)		Analytical Lab: Harrogate			
Timepoint	Statistic	Male		P-value ^a	
		Smokers	Non-Smokers		
Week 1	N	18		NA	32
	MEAN, GEO MEAN	74.8, 59.1			74.2, 59.6
	SD, SE	53.02, 12.50			52.55, 9.29
	MEDIAN	59.0			58.2
	MIN, MAX	6.3, 200.9			9.1, 262.7
	5%, 95%	6.3, 200.9			15.1, 162.2
	# of BLQ/ALQ Values	0/0			0/0
Week 2	N	18		NA	31
	MEAN, GEO MEAN	116.5, 70.3			87.7, 71.8
	SD, SE	185.29, 43.67			61.81, 11.10
	MEDIAN	72.0			67.8
	MIN, MAX	5.2, 843.9			22.1, 294.1
	5%, 95%	5.2, 843.9			30.9, 238.9
	# of BLQ/ALQ Values	0/0			0/0
Week 3	N	17		NA	29
	MEAN, GEO MEAN	108.7, 68.5			80.3, 65.7
	SD, SE	127.80, 31.00			61.09, 11.34
	MEDIAN	68.5			62.0
	MIN, MAX	2.0, 571.6			20.8, 322.5
	5%, 95%	2.0, 571.6			29.5, 175.1
	# of BLQ/ALQ Values	0/0			0/0
Overall ^b	N	18		NA	32
	MEAN, GEO MEAN	99.2, 68.4			80.5, 67.6
	SD, SE	115.70, 27.27			54.54, 9.64
	MEDIAN	65.7			63.1
	MIN, MAX	4.5, 538.8			19.3, 293.1
	5%, 95%	4.5, 538.8			31.8, 161.5

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234" will be used as "1.234" for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438701

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 42 of 264)

Biomarker: Cotinine ((nmol/L)/cigarette per day) Analytical Lab: Harrogate

Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	424.5, 335.2			421.2, 338.2		
	SD, SE	300.93, 70.93			298.22, 52.72		
	MEDIAN	334.6			330.1		
	MIN, MAX	35.9, 1140.3			51.7, 1490.7		
	5%, 95%	35.9, 1140.3			85.7, 920.5		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	661.1, 399.0			497.6, 407.4		
	SD, SE	1051.52, 247.85			350.77, 63.00		
	MEDIAN	408.4			385.0		
	MIN, MAX	29.3, 4789.2			125.6, 1668.8		
	5%, 95%	29.3, 4789.2			175.5, 1355.9		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	616.9, 388.9			455.8, 372.9		
	SD, SE	725.28, 175.91			346.75, 64.39		
	MEDIAN	388.5			352.1		
	MIN, MAX	11.5, 3243.9			118.0, 1830.3		
	5%, 95%	11.5, 3243.9			167.4, 993.8		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	562.7, 388.1			456.8, 383.6		
	SD, SE	656.63, 154.77			309.55, 54.72		
	MEDIAN	372.5			358.0		
	MIN, MAX	25.6, 3057.8			109.8, 1663.3		
	5%, 95%	25.6, 3057.8			180.6, 916.8		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438702

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 43 of 264)

Biomarker: Cotinine-N-glucuronide (nmol/L)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	12775.686, 5928.173	12.447, NA		11946.851, 6284.199	3.616, NA	
	SD, SE	15906.0495, 3749.0918	24.9161, 4.5490		12768.6173, 2257.1940	7.5616, 1.2781	
	MEDIAN	6149.147	2.554		6802.623	0.000	
	MIN, MAX	71.505, 58435.475	0.000, 121.445		103.285, 57183.003	0.000, 31.780	
	5%, 95%	71.505, 58435.475	0.000, 49.373		193.518, 41739.058	0.000, 23.268	
	# of BLQ/ALQ Values	0/0	19/0		0/0	30/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	12429.228, 6666.938	14.169, NA		15118.109, 8074.155	4.232, NA	
	SD, SE	14017.9902, 3304.0720	24.9605, 4.5571		16526.0875, 2968.1729	7.1484, 1.2083	
	MEDIAN	8346.791	2.554		6741.333	0.000	
	MIN, MAX	73.775, 60546.008	0.000, 92.503		286.588, 77152.193	0.000, 24.970	
	5%, 95%	73.775, 60546.008	0.000, 71.505		310.423, 42263.995	0.000, 20.430	
	# of BLQ/ALQ Values	0/0	18/0		0/0	29/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	9575.361, 5758.281	8.929, NA		12155.165, 7318.112	2.659, NA	
	SD, SE	7119.6849, 1726.7772	16.0375, 2.9280		10191.6726, 1892.5461	6.5387, 1.1052	
	MEDIAN	8817.815	1.987		8595.355	0.000	
	MIN, MAX	81.153, 23770.305	0.000, 78.883		160.035, 37456.135	0.000, 28.943	
	5%, 95%	81.153, 23770.305	0.000, 36.320		900.623, 29846.528	0.000, 19.863	
	# of BLQ/ALQ Values	0/0	18/0		0/0	32/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	11720.704, 6790.708	11.848, NA		12733.509, 7363.967	3.502, NA	
	SD, SE	10966.1100, 2584.7369	18.0395, 3.2936		12218.3039, 2159.9114	6.1746, 1.0437	
	MEDIAN	9090.310	4.351		7428.198	0.568	
	MIN, MAX	75.478, 44996.319	0.000, 74.910		221.325, 53864.641	0.000, 23.268	
	5%, 95%	75.478, 44996.319	0.000, 52.400		430.165, 31626.019	0.000, 23.079	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234* for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438703

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 44 of 264)

Biomarker: Cotinine-N-glucuronide ((nmol/L)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	810.916, 467.157			734.934, 475.851		
	SD, SE	921.7349, 217.2550			688.4226, 121.6971		
	MEDIAN	456.287			586.977		
	MIN, MAX	23.835, 3712.490			51.643, 2599.227		
	5%, 95%	23.835, 3712.490			64.506, 2470.157		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	850.290, 528.079			1034.785, 658.445		
	SD, SE	723.5844, 170.5505			992.6234, 178.2804		
	MEDIAN	793.291			590.995		
	MIN, MAX	24.592, 2367.300			103.474, 3857.610		
	5%, 95%	24.592, 2367.300			126.571, 3761.075		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	949.137, 541.612			826.740, 529.423		
	SD, SE	1090.5024, 264.4857			717.1538, 133.1721		
	MEDIAN	533.582			606.714		
	MIN, MAX	27.051, 3961.718			32.007, 2846.864		
	5%, 95%	27.051, 3961.718			100.391, 2497.076		
	# of BLQ/ALQ Values	0/0			0/0		
Overall*	N	18		NA	32		NA
	MEAN, GEO MEAN	866.997, 562.016			862.992, 577.351		
	SD, SE	720.6777, 169.8654			745.8771, 131.8537		
	MEDIAN	667.112			698.097		
	MIN, MAX	25.159, 2522.024			66.662, 3026.032		
	5%, 95%	25.159, 2522.024			128.640, 2758.029		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438704

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 45 of 264)

Biomarker: Cotinine-N-glucuronide (nmol/24hr) Analytical Lab: Harrogate

Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	17099.631, 9702.851	18.077, NA		17856.776, 11002.526	7.214, NA	
	SD, SE	16437.8673, 3874.4425	31.1255, 5.6827		14914.8964, 2636.6061	17.8516, 3.0175	
	MEDIAN	14284.827	2.645		13051.204	0.000	
	MIN, MAX	100.822, 68661.683	0.000, 106.872		284.034, 60518.854	0.000, 75.621	
	5%, 95%	100.822, 68661.683	0.000, 106.084		561.202, 52173.823	0.000, 72.395	
	# of BLQ/ALQ Values	0/0	19/0		0/0	30/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	15578.821, 9437.531	23.010, NA		19694.105, 13152.196	8.773, NA	
	SD, SE	12680.2255, 2988.7578	43.7941, 7.9957		15548.2161, 2792.5421	15.3683, 2.5977	
	MEDIAN	14129.657	2.566		14973.828	0.000	
	MIN, MAX	66.398, 54491.407	0.000, 203.789		453.218, 68665.452	0.000, 54.934	
	5%, 95%	66.398, 54491.407	0.000, 103.001		523.023, 55851.960	0.000, 44.129	
	# of BLQ/ALQ Values	0/0	18/0		0/0	29/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	17262.737, 9735.883	15.560, NA		18129.673, 12558.609	5.147, NA	
	SD, SE	13557.2368, 3288.1129	27.1386, 4.9548		11936.9451, 2216.6351	13.0225, 2.2012	
	MEDIAN	14321.885	3.388		17400.969	0.000	
	MIN, MAX	85.048, 48342.568	0.000, 105.328		224.049, 48692.976	0.000, 52.637	
	5%, 95%	85.048, 48342.568	0.000, 102.548		1675.159, 37176.403	0.000, 50.216	
	# of BLQ/ALQ Values	0/0	18/0		0/0	32/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	16709.630, 10031.393	18.882, NA		18082.402, 12337.082	7.045, NA	
	SD, SE	13467.4893, 3174.3177	29.3085, 5.3510		13234.2559, 2339.5080	13.1343, 2.2201	
	MEDIAN	16733.542	4.780		15450.516	0.499	
	MIN, MAX	84.089, 57165.219	0.000, 104.966		412.823, 46589.501	0.000, 48.839	
	5%, 95%	84.089, 57165.219	0.000, 97.288		827.405, 46579.291	0.000, 42.815	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 46 of 264)

Biomarker: Cotinine-N-glucuronide ((nmol/24hr)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value*	Smokers	Non-Smokers	P-value*
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	1093.850, 764.612			1145.880, 833.131		
	SD, SE	885.5225, 208.7197			1096.2961, 193.7996		
	MEDIAN	830.688			855.081		
	MIN, MAX	33.607, 3229.867			90.023, 6051.885		
	5%, 95%	33.607, 3229.867			142.017, 3069.048		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	1075.089, 747.534			1451.953, 1072.558		
	SD, SE	811.5326, 191.2801			1335.1913, 239.8074		
	MEDIAN	860.829			1020.252		
	MIN, MAX	22.133, 3361.488			151.073, 6205.773		
	5%, 95%	22.133, 3361.488			443.000, 4389.603		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	1362.232, 915.736			1216.198, 908.543		
	SD, SE	1000.7132, 242.7086			847.6669, 157.4078		
	MEDIAN	1273.684			995.011		
	MIN, MAX	28.349, 4080.569			44.810, 3246.198		
	5%, 95%	28.349, 4080.569			196.849, 3033.231		
	# of BLQ/ALQ Values	0/0			0/0		
Overall*	N	18		NA	32		NA
	MEAN, GEO MEAN	1169.703, 839.791			1268.057, 971.106		
	SD, SE	760.8145, 179.3257			1006.9570, 178.0057		
	MEDIAN	909.152			922.614		
	MIN, MAX	28.030, 2578.398			127.650, 5059.513		
	5%, 95%	28.030, 2578.398			276.448, 2748.884		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438706

Final Draft: 22 October 2003

Page 737 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 47 of 264)

Biomarker: Cotinine-N-glucuronide (nmol/mg Creatinine) Analytical Lab: Harrogate

Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	11.128, 7.340	0.011, NA		14.577, 9.595	0.006, NA	
	SD, SE	7.4252, 1.7501	0.0210, 0.0038		10.3373, 1.8274	0.0136, 0.0023	
	MEDIAN	10.682	0.002		14.598	0.000	
	MIN, MAX	0.095, 27.231	0.000, 0.075		0.236, 37.108	0.000, 0.055	
	5%, 95%	0.095, 27.231	0.000, 0.066		0.507, 36.704	0.000, 0.049	
	# of BLQ/ALQ Values	0/0	19/0		0/0	30/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	10.408, 6.935	0.016, NA		15.196, 10.444	0.007, NA	
	SD, SE	6.8410, 1.6124	0.0371, 0.0068		11.8468, 2.1277	0.0122, 0.0021	
	MEDIAN	10.268	0.002		13.259	0.000	
	MIN, MAX	0.074, 26.176	0.000, 0.195		0.392, 53.877	0.000, 0.045	
	5%, 95%	0.074, 26.176	0.000, 0.058		0.522, 38.730	0.000, 0.039	
	# of BLQ/ALQ Values	0/0	18/0		0/0	29/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	11.268, 7.027	0.008, NA		15.296, 10.711	0.005, NA	
	SD, SE	7.7146, 1.8711	0.0151, 0.0028		11.2894, 2.0964	0.0138, 0.0023	
	MEDIAN	9.472	0.002		14.211	0.000	
	MIN, MAX	0.075, 22.527	0.000, 0.060		0.264, 49.743	0.000, 0.067	
	5%, 95%	0.075, 22.527	0.000, 0.057		1.668, 40.962	0.000, 0.035	
	# of BLQ/ALQ Values	0/0	18/0		0/0	32/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	10.959, 7.253	0.012, NA		14.900, 10.481	0.006, NA	
	SD, SE	7.0907, 1.6713	0.0208, 0.0038		10.5712, 1.8687	0.0119, 0.0020	
	MEDIAN	11.094	0.002		14.601	0.000	
	MIN, MAX	0.081, 23.794	0.000, 0.091		0.388, 38.906	0.000, 0.049	
	5%, 95%	0.081, 23.794	0.000, 0.061		0.809, 38.799	0.000, 0.038	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438707

Final Draft: 22 October 2003

Page 738 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 48 of 264)

Biomarker: Cotinine-N-glucuronide ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	0.885, 0.379			0.918, 0.727		
	SD, SE	0.8592, 0.2025			0.6984, 0.1235		
	MEDIAN	0.503			0.761		
	MIN, MAX	0.032, 2.946			0.118, 3.670		
	5%, 95%	0.032, 2.946			0.169, 2.137		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	0.955, 0.550			1.108, 0.852		
	SD, SE	1.4836, 0.3497			0.9291, 0.1669		
	MEDIAN	0.550			0.839		
	MIN, MAX	0.025, 6.653			0.131, 4.303		
	5%, 95%	0.025, 6.653			0.403, 2.843		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	0.980, 0.661			1.069, 0.775		
	SD, SE	0.8366, 0.2029			1.0407, 0.1933		
	MEDIAN	0.722			0.772		
	MIN, MAX	0.025, 3.082			0.053, 5.120		
	5%, 95%	0.025, 3.082			0.209, 3.316		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	0.933, 0.611			1.044, 0.824		
	SD, SE	0.9816, 0.2314			0.8336, 0.1474		
	MEDIAN	0.617			0.830		
	MIN, MAX	0.027, 4.227			0.118, 4.364		
	5%, 95%	0.027, 4.227			0.325, 2.594		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438708

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 49 of 264)

Biomarker: Nicotine (µg/24hr)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	1685.189, 1137.843	7.867, 2.456		1778.702, 1034.077	2.202, 1.896	
	SD, SE	1101.8218, 259.7019	19.3657, 3.5357		1601.2984, 283.0722	1.5415, 0.2606	
	MEDIAN	1444.194	1.619		1281.883	1.900	
	MIN, MAX	18.048, 3521.714	0.530, 93.100		76.527, 5245.860	0.570, 9.792	
	5%, 95%	18.048, 3521.714	0.780, 58.311		83.814, 5088.650	0.800, 3.350	
	# of BLQ/ALQ Values	0/0	18/0		0/0	33/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	1746.577, 1234.839	12.592, 2.332		1840.681, 1134.230	2.299, 2.000	
	SD, SE	992.7277, 233.9882	54.8383, 10.0121		1545.7478, 277.6245	1.4079, 0.2380	
	MEDIAN	1592.530	1.680		1490.076	2.150	
	MIN, MAX	10.980, 3494.785	0.625, 302.670		81.312, 5904.527	0.660, 8.514	
	5%, 95%	10.980, 3494.785	0.815, 12.512		94.792, 4764.320	0.750, 4.585	
	# of BLQ/ALQ Values	0/0	22/0		0/0	32/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	2172.224, 1008.701	2.702, 2.114		1952.179, 1443.640	2.116, 1.974	
	SD, SE	2176.7037, 527.9282	2.5477, 0.4651		1234.0737, 229.1617	0.8139, 0.1376	
	MEDIAN	1269.580	1.900		1954.260	2.030	
	MIN, MAX	5.450, 6614.080	0.750, 13.650		55.800, 4262.175	0.940, 4.740	
	5%, 95%	5.450, 6614.080	0.750, 7.259		417.200, 4138.428	0.990, 3.350	
	# of BLQ/ALQ Values	0/0	23/0		0/0	34/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	1878.760, 1253.987	7.721, 2.668		1799.419, 1211.436	2.206, 2.011	
	SD, SE	1166.6214, 274.9753	22.2784, 4.0675		1353.6781, 239.2987	0.9890, 0.1672	
	MEDIAN	1786.222	1.863		1574.517	2.150	
	MIN, MAX	11.493, 3792.219	0.793, 121.310		85.660, 4824.558	0.967, 5.163	
	5%, 95%	11.493, 3792.219	0.865, 33.074		130.092, 4299.995	0.980, 4.270	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438709

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 50 of 264)

Biomarker: Nicotine (nmol/24hr)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	10389.190, 7014.802	48.501, 15.139		10965.699, 6375.083	13.578, 11.689	
	SD, SE	6792.7315, 1601.0622	119.3893, 21.7974		9872.0048, 1745.1404	9.5034, 1.6064	
	MEDIAN	8903.456	9.978		7902.809	11.714	
	MIN, MAX	111.266, 21711.367	3.267, 573.962		471.789, 32340.727	3.514, 60.368	
	5%, 95%	111.266, 21711.367	4.809, 359.487		516.713, 31371.527	4.932, 20.653	
	# of BLQ/ALQ Values	0/0	18/0		0/0	33/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	10767.648, 7612.786	77.631, 14.378		11347.798, 6992.529	14.176, 12.327	
	SD, SE	6120.1664, 1442.5371	338.0780, 61.7243		9529.5349, 1711.5550	8.6798, 1.4671	
	MEDIAN	9817.948	10.357		9186.319	13.255	
	MIN, MAX	67.692, 21545.350	3.853, 1865.961		501.288, 36401.409	4.069, 52.489	
	5%, 95%	67.692, 21545.350	5.024, 77.136		584.393, 29372.033	4.624, 28.267	
	# of BLQ/ALQ Values	0/0	22/0		0/0	32/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	13391.759, 6218.636	16.659, 13.035		12035.184, 8900.039	13.046, 12.167	
	SD, SE	13419.3783, 3254.6773	15.7067, 2.8676		7608.0647, 1412.7821	5.0180, 0.8482	
	MEDIAN	7826.961	11.714		12048.013	12.515	
	MIN, MAX	33.599, 40775.803	4.624, 84.152		344.007, 26276.309	5.795, 29.222	
	5%, 95%	33.599, 40775.803	4.624, 44.752		2572.038, 25513.409	6.103, 20.653	
	# of BLQ/ALQ Values	0/0	23/0		0/0	34/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	11582.557, 7730.816	47.597, 16.446		11093.418, 7468.500	13.600, 12.399	
	SD, SE	7192.2206, 1695.2226	137.3465, 25.0759		8345.4257, 1475.2768	6.0976, 1.0307	
	MEDIAN	11012.056	11.484		9706.899	13.255	
	MIN, MAX	70.852, 23379.028	4.891, 747.878		528.091, 29743.402	5.960, 31.832	
	5%, 95%	70.852, 23379.028	5.331, 203.904		802.015, 26509.469	6.042, 26.323	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics).

PM3006438710

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 51 of 264)

Biomarker: Nicotine ((ug/24hr)/cigarette per day) Analytical Lab: Harrogate

Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	134.044, 89.665			107.059, 78.302		
	SD, SE	131.8900, 31.0868			82.0618, 14.5066		
	MEDIAN	114.896			86.057		
	MIN, MAX	6.016, 590.746			14.337, 363.475		
	5%, 95%	6.016, 590.746			16.763, 244.020		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	196.148, 97.810			129.311, 92.496		
	SD, SE	390.9936, 92.1581			102.5182, 18.4128		
	MEDIAN	100.419			85.370		
	MIN, MAX	3.660, 1747.393			16.262, 376.716		
	5%, 95%	3.660, 1747.393			16.394, 360.360		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	142.448, 94.877			131.410, 104.439		
	SD, SE	96.6999, 23.4532			87.7583, 16.2963		
	MEDIAN	145.831			107.140		
	MIN, MAX	1.817, 376.203			13.950, 422.898		
	5%, 95%	1.817, 376.203			29.233, 275.895		
	# of BLQ/ALQ Values	0/0			0/0		
Overall†	N	18		NA	32		NA
	MEAN, GEO MEAN	157.245, 104.761			119.177, 97.804		
	SD, SE	181.1319, 42.6932			75.5788, 13.3606		
	MEDIAN	121.480			96.236		
	MIN, MAX	3.831, 849.365			22.234, 287.989		
	5%, 95%	3.831, 849.365			40.787, 281.914		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

† Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234" will be used as "1.234") for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438711

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 52 of 264)

Biomarker: Nicotine ((nmol/24hr)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	826.379, 552.787			660.019, 482.733		
	SD, SE	813.1014, 191.6498			505.9107, 89.4332		
	MEDIAN	708.333			530.544		
	MIN, MAX	37.089, 3641.947			88.388, 2240.823		
	5%, 95%	37.089, 3641.947			103.343, 1504.383		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	1209.249, 602.998			797.203, 570.239		
	SD, SE	2410.4749, 568.1544			632.0241, 113.5149		
	MEDIAN	619.084			526.308		
	MIN, MAX	22.564, 10772.675			100.258, 2322.453		
	5%, 95%	22.564, 10772.675			101.072, 2221.619		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	878.195, 584.913			810.142, 643.866		
	SD, SE	596.1545, 144.5887			541.0306, 100.4669		
	MEDIAN	899.047			660.518		
	MIN, MAX	11.200, 2319.289			86.002, 2607.168		
	5%, 95%	11.200, 2319.289			180.219, 1700.894		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	969.418, 645.850			734.727, 602.959		
	SD, SE	1116.6774, 263.2034			465.9432, 82.3679		
	MEDIAN	748.925			593.294		
	MIN, MAX	23.618, 5236.332			137.071, 1775.452		
	5%, 95%	23.618, 5236.332			251.451, 1737.999		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438712

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2.2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 53 of 264)

Biomarker: Nicotine (µg/mg Creatinine)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	1.564, 0.861	0.005, NA		1.543, 0.902	0.002, NA	
	SD, SE	1.9898, 0.4690	0.0106, 0.0019		1.4185, 0.2508	0.0022, 0.0004	
	MEDIAN	1.038	0.001		1.072	0.002	
	MIN, MAX	0.017, 8.892	0.000, 0.044		0.050, 5.613	0.000, 0.014	
	5%, 95%	0.017, 8.892	0.000, 0.041		0.071, 5.001	0.001, 0.003	
	# of BLQ/ALQ Values	0/0	18/0		0/0	33/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	1.463, 0.906	0.011, NA		1.458, 0.901	0.002, NA	
	SD, SE	1.5262, 0.3597	0.0525, 0.0096		1.3118, 0.2356	0.0014, 0.0002	
	MEDIAN	1.135	0.001		1.262	0.002	
	MIN, MAX	0.012, 6.916	0.000, 0.289		0.064, 5.630	0.000, 0.008	
	5%, 95%	0.012, 6.916	0.000, 0.014		0.071, 4.633	0.001, 0.004	
	# of BLQ/ALQ Values	0/0	22/0		0/0	32/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	1.392, 0.730	0.001, NA		1.667, 1.232	0.002, 0.002	
	SD, SE	1.1591, 0.2811	0.0015, 0.0003		1.1687, 0.2170	0.0010, 0.0002	
	MEDIAN	1.218	0.001		1.493	0.002	
	MIN, MAX	0.005, 4.246	0.000, 0.008		0.056, 5.060	0.001, 0.005	
	5%, 95%	0.005, 4.246	0.000, 0.003		0.357, 4.177	0.001, 0.004	
	# of BLQ/ALQ Values	0/0	23/0		0/0	34/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	1.477, 0.920	0.006, NA		1.547, 1.032	0.002, NA	
	SD, SE	1.3164, 0.3103	0.0201, 0.0037		1.2482, 0.2207	0.0013, 0.0002	
	MEDIAN	1.237	0.001		1.362	0.002	
	MIN, MAX	0.011, 5.866	0.000, 0.111		0.061, 5.434	0.000, 0.007	
	5%, 95%	0.011, 5.866	0.000, 0.015		0.119, 4.066	0.001, 0.004	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics).

PM3006438713

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 54 of 264)

Biomarker: Nicotine (nmol/mg Creatinine)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value*	Smokers	Non-Smokers	P-value*
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	9.640, 5.307	0.028, NA		9.514, 5.558	0.012, NA	
	SD, SE	12.2671, 2.8914	0.0654, 0.0119		8.7453, 1.5460	0.0135, 0.0023	
	MEDIAN	6.396	0.006		6.606	0.012	
	MIN, MAX	0.105, 54.819	0.000, 0.271		0.308, 34.604	0.000, 0.086	
	5%, 95%	0.105, 54.819	0.000, 0.253		0.438, 30.831	0.006, 0.018	
	# of BLQ/ALQ Values	0/0	18/0		0/0	33/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	9.017, 5.588	0.070, NA		8.986, 5.553	0.012, NA	
	SD, SE	9.4091, 2.2178	0.3236, 0.0591		8.0873, 1.4525	0.0088, 0.0015	
	MEDIAN	6.994	0.006		7.780	0.012	
	MIN, MAX	0.074, 42.637	0.000, 1.782		0.395, 34.709	0.000, 0.049	
	5%, 95%	0.074, 42.637	0.000, 0.086		0.438, 28.562	0.006, 0.025	
	# of BLQ/ALQ Values	0/0	22/0		0/0	32/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	8.580, 4.502	0.009, NA		10.277, 7.593	0.012, 0.010	
	SD, SE	7.1459, 1.7331	0.0089, 0.0016		7.2053, 1.3380	0.0062, 0.0010	
	MEDIAN	7.509	0.006		9.204	0.012	
	MIN, MAX	0.031, 26.177	0.000, 0.049		0.345, 31.195	0.006, 0.031	
	5%, 95%	0.031, 26.177	0.000, 0.018		2.201, 25.751	0.006, 0.025	
	# of BLQ/ALQ Values	0/0	23/0		0/0	34/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	9.107, 5.684	0.036, NA		9.537, 6.362	0.012, 0.010	
	SD, SE	8.1155, 1.9128	0.1234, 0.0225		7.6954, 1.3604	0.0073, 0.0012	
	MEDIAN	7.627	0.007		8.394	0.010	
	MIN, MAX	0.070, 36.164	0.000, 0.682		0.373, 33.503	0.002, 0.041	
	5%, 95%	0.070, 36.164	0.002, 0.094		0.734, 25.067	0.006, 0.025	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438714

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 55 of 264)

Biomarker: Nicotine ((µg/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	0.176, 0.068			0.091, 0.068		
	SD, SE	0.4043, 0.0953			0.0629, 0.0111		
	MEDIAN	0.074			0.069		
	MIN, MAX	0.006, 1.778			0.011, 0.251		
	5%, 95%	0.006, 1.778			0.014, 0.187		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	0.262, 0.072			0.102, 0.074		
	SD, SE	0.7989, 0.1883			0.0764, 0.0137		
	MEDIAN	0.062			0.065		
	MIN, MAX	0.004, 3.458			0.013, 0.250		
	5%, 95%	0.004, 3.458			0.013, 0.244		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	0.105, 0.070			0.112, 0.089		
	SD, SE	0.0828, 0.0201			0.0733, 0.0136		
	MEDIAN	0.094			0.090		
	MIN, MAX	0.002, 0.358			0.014, 0.287		
	5%, 95%	0.002, 0.358			0.028, 0.255		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	0.180, 0.078			0.101, 0.083		
	SD, SE	0.4224, 0.0996			0.0618, 0.0109		
	MEDIAN	0.081			0.079		
	MIN, MAX	0.004, 1.865			0.016, 0.228		
	5%, 95%	0.004, 1.865			0.027, 0.227		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438715

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 56 of 264)

Biomarker: Nicotine (nmol/mg Creatinine)/cigarette per day Analytical Lab: Harrogate

Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	1.084, 0.418			0.558, 0.421		
	SD, SE	2.4930, 0.5876			0.3876, 0.0685		
	MEDIAN	0.452			0.427		
	MIN, MAX	0.035, 10.964			0.067, 1.550		
	5%, 95%	0.035, 10.964			0.088, 1.153		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	1.617, 0.443			0.628, 0.453		
	SD, SE	4.9253, 1.1609			0.4711, 0.0846		
	MEDIAN	0.382			0.401		
	MIN, MAX	0.025, 21.319			0.078, 1.541		
	5%, 95%	0.025, 21.319			0.079, 1.504		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	0.646, 0.423			0.692, 0.549		
	SD, SE	0.5108, 0.1239			0.4520, 0.0839		
	MEDIAN	0.581			0.557		
	MIN, MAX	0.010, 2.207			0.086, 1.771		
	5%, 95%	0.010, 2.207			0.171, 1.570		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	1.112, 0.477			0.624, 0.513		
	SD, SE	2.6039, 0.6138			0.3811, 0.0674		
	MEDIAN	0.500			0.490		
	MIN, MAX	0.023, 11.497			0.096, 1.408		
	5%, 95%	0.023, 11.497			0.169, 1.399		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438716

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 57 of 264)

Biomarker: Nicotine (ng/mL)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	1071.6, 695.2	3.4, 1.7		1181.3, 590.6	1.2, 1.1	
	SD, SE	894.09, 210.74	6.00, 1.10		1369.23, 242.05	0.98, 0.17	
	MEDIAN	810.1	1.0		597.3	1.0	
	MIN, MAX	12.8, 3752.0	1.0, 24.5		32.7, 6329.6	1.0, 6.8	
	5%, 95%	12.8, 3752.0	1.0, 20.9		45.8, 3781.9	1.0, 1.2	
	# of BLQ/ALQ Values	0/0	18/0		0/0	33/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	1278.9, 872.3	5.1, 1.5		1226.1, 696.3	1.1, 1.1	
	SD, SE	900.59, 212.27	19.15, 3.50		1429.99, 256.83	0.58, 0.10	
	MEDIAN	993.7	1.0		730.7	1.0	
	MIN, MAX	12.2, 3489.6	1.0, 106.2		67.2, 6634.3	1.0, 4.3	
	5%, 95%	12.2, 3489.6	1.0, 5.7		83.5, 4961.8	1.0, 2.1	
	# of BLQ/ALQ Values	0/0	22/0		0/0	32/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	1075.5, 596.6	1.5, 1.2		1220.1, 841.2	1.0, 1.0	
	SD, SE	898.87, 218.01	1.80, 0.33		965.31, 179.25	0.07, 0.01	
	MEDIAN	820.2	1.0		1123.3	1.0	
	MIN, MAX	5.2, 3006.4	1.0, 10.5		30.0, 3630.2	1.0, 1.4	
	5%, 95%	5.2, 3006.4	1.0, 4.0		291.1, 3563.7	1.0, 1.0	
	# of BLQ/ALQ Values	0/0	23/0		0/0	34/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	1160.2, 803.0	3.3, 1.6		1171.2, 714.3	1.1, 1.1	
	SD, SE	733.75, 172.95	7.75, 1.41		1158.40, 204.78	0.43, 0.07	
	MEDIAN	947.1	1.0		705.4	1.0	
	MIN, MAX	10.1, 2449.9	1.0, 42.7		65.6, 5531.4	1.0, 3.3	
	5%, 95%	10.1, 2449.9	1.0, 9.9		69.4, 3012.0	1.0, 2.1	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438717

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 58 of 264)

Biomarker: Nicotine (nmol/L)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	6606.6, 4285.8	20.9, 10.3		7282.7, 3641.2	7.3, 6.6	
	SD, SE	5512.07, 1299.21	36.96, 6.75		8441.30, 1492.23	6.03, 1.02	
	MEDIAN	4994.3	6.2		3682.4	6.2	
	MIN, MAX	78.9, 23131.1	6.2, 151.0		201.6, 39022.0	6.2, 41.9	
	5%, 95%	78.9, 23131.1	6.2, 128.8		282.4, 23315.4	6.2, 7.4	
	# of BLQ/ALQ Values	0/0	18/0		0/0	33/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	7884.4, 5377.8	31.2, 9.3		7559.2, 4292.7	7.0, 6.6	
	SD, SE	5552.14, 1308.65	118.03, 21.55		8815.87, 1583.38	3.58, 0.61	
	MEDIAN	6126.2	6.2		4504.8	6.2	
	MIN, MAX	75.2, 21513.4	6.2, 654.7		414.3, 40900.5	6.2, 26.5	
	5%, 95%	75.2, 21513.4	6.2, 35.1		514.8, 30589.5	6.2, 12.9	
	# of BLQ/ALQ Values	0/0	22/0		0/0	32/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	6630.4, 3678.3	9.3, 7.5		7522.2, 5186.3	6.3, 6.3	
	SD, SE	5541.54, 1344.02	11.07, 2.02		5951.14, 1105.10	0.41, 0.07	
	MEDIAN	5056.5	6.2		6925.1	6.2	
	MIN, MAX	32.1, 18534.5	6.2, 64.7		185.0, 22380.2	6.2, 8.6	
	5%, 95%	32.1, 18534.5	6.2, 24.7		1794.6, 21970.2	6.2, 6.2	
	# of BLQ/ALQ Values	0/0	23/0		0/0	34/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	7152.5, 4949.8	20.4, 10.2		7220.5, 4403.2	6.8, 6.6	
	SD, SE	4573.60, 1066.22	47.74, 8.72		7141.56, 1762.46	2.61, 0.44	
	MEDIAN	5838.7	6.3		4348.7	6.2	
	MIN, MAX	62.1, 15103.7	6.2, 263.2		404.2, 34100.9	6.2, 20.3	
	5%, 95%	62.1, 15103.7	6.2, 60.8		427.6, 18569.2	6.2, 13.0	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438718

Final Draft: 22 October 2003

Page 749 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 59 of 264)

Biomarker: Nicotine ((ng/mL)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	85.3, 54.8			68.4, 44.7		
	SD, SE	88.05, 20.75			64.18, 11.35		
	MEDIAN	55.4			41.8		
	MIN, MAX	4.3, 312.7			8.1, 287.7		
	5%, 95%	4.3, 312.7			9.2, 189.1		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	142.9, 69.1			81.0, 56.8		
	SD, SE	257.04, 60.59			75.59, 13.58		
	MEDIAN	65.7			49.5		
	MIN, MAX	4.1, 1127.4			13.4, 331.7		
	5%, 95%	4.1, 1127.4			16.0, 236.3		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	87.1, 56.0			85.2, 60.9		
	SD, SE	86.17, 20.90			71.13, 13.21		
	MEDIAN	71.2			62.8		
	MIN, MAX	1.7, 374.9			7.5, 316.8		
	5%, 95%	1.7, 374.9			14.7, 242.0		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	105.2, 66.6			75.9, 57.5		
	SD, SE	133.46, 31.46			61.71, 10.91		
	MEDIAN	71.8			50.7		
	MIN, MAX	3.4, 603.3			14.5, 287.1		
	5%, 95%	3.4, 603.3			20.1, 209.9		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438719

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 60 of 264)

Biomarker: Nicotine (nmol/L/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	525.5, 337.7			421.6, 275.7		
	SD, SE	542.84, 127.95			395.69, 69.95		
	MEDIAN	341.2			257.6		
	MIN, MAX	26.3, 1927.6			49.9, 1773.7		
	5%, 95%	26.3, 1927.6			56.5, 1165.8		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	880.7, 426.0			499.1, 350.1		
	SD, SE	1584.59, 373.49			465.96, 83.69		
	MEDIAN	404.6			305.0		
	MIN, MAX	25.1, 6950.1			82.9, 2045.0		
	5%, 95%	25.1, 6950.1			98.6, 1456.6		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	536.7, 346.0			525.1, 375.2		
	SD, SE	531.24, 128.84			438.50, 81.43		
	MEDIAN	438.7			387.3		
	MIN, MAX	10.7, 2311.4			46.3, 1952.9		
	5%, 95%	10.7, 2311.4			90.3, 1492.0		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	648.6, 410.4			467.9, 354.1		
	SD, SE	822.81, 193.94			380.53, 67.27		
	MEDIAN	442.3			312.3		
	MIN, MAX	20.7, 3719.4			89.0, 1770.2		
	5%, 95%	20.7, 3719.4			123.7, 1294.1		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438720

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 61 of 264)

Biomarker: Nicotine-N-glucuronide (nmol/L)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	28	<.0001	31	34	<.0001
	MEAN, GEO MEAN	3185.833, 1315.053	3.369, NA		2857.657, 1385.609	0.526, NA	
	SD, SE	4046.7969, 953.8392	5.8234, 1.1005		3716.0670, 667.4253	1.5264, 0.2618	
	MEDIAN	1437.370	0.000		1405.004	0.000	
	MIN, MAX	17.879, 12968.078	0.000, 22.811		59.184, 17624.502	0.000, 6.782	
	5%, 95%	17.879, 12968.078	0.000, 18.495		71.514, 10892.322	0.000, 4.932	
	# of BLQ/ALQ Values	0/0	18/0		0/0	33/0	
Week 2	N	17	29	<.0001	31	34	<.0001
	MEAN, GEO MEAN	3220.379, 1984.938	5.166, NA		3586.081, 1633.399	0.399, NA	
	SD, SE	3208.1796, 778.0978	18.3997, 3.4167		4914.8761, 882.7378	1.7363, 0.2978	
	MEDIAN	1499.945	0.000		1458.639	0.000	
	MIN, MAX	330.444, 10055.115	0.000, 99.257		68.432, 25269.102	0.000, 9.864	
	5%, 95%	330.444, 10055.115	0.000, 11.714		106.038, 10255.478	0.000, 2.466	
	# of BLQ/ALQ Values	0/0	22/0		0/0	32/0	
Week 3	N	16	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	2390.017, 1334.459	2.589, NA		3029.460, 1504.195	0.247, NA	
	SD, SE	1832.9412, 458.2353	5.7411, 1.0482		2699.1081, 501.2118	0.8745, 0.1478	
	MEDIAN	2286.599	0.000		2594.232	0.000	
	MIN, MAX	27.126, 5382.662	0.000, 28.976		12.330, 8494.754	0.000, 4.316	
	5%, 95%	27.126, 5382.662	0.000, 11.714		17.879, 8343.711	0.000, 2.466	
	# of BLQ/ALQ Values	0/0	23/0		0/0	34/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	2837.219, 1507.004	3.689, NA		3047.122, 1633.131	0.393, NA	
	SD, SE	2853.8907, 673.1399	7.5385, 1.3763		3367.0203, 595.2107	1.1359, 0.1920	
	MEDIAN	1684.176	0.103		1332.873	0.000	
	MIN, MAX	22.503, 9135.914	0.000, 36.579		68.432, 14522.685	0.000, 5.549	
	5%, 95%	22.503, 9135.914	0.000, 19.112		98.640, 11621.847	0.000, 3.699	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438721

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 62 of 264)

Biomarker: Nicotine-N-glucuronide (nmol/L/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	31		NA
	MEAN, GEO MEAN	209.881, 103.631			172.883, 107.735		
	SD, SE	265.7647, 62.6413			203.3168, 36.5168		
	MEDIAN	99.003			113.411		
	MIN, MAX	5.960, 962.254			14.180, 1036.735		
	5%, 95%	5.960, 962.254			20.933, 495.106		
Week 2	# of BLQ/ALQ Values	0/0		NA	0/0		NA
	N	17			31		
	MEAN, GEO MEAN	225.933, 144.480			243.814, 133.203		
	SD, SE	209.2341, 50.7467			297.5609, 53.4435		
	MEDIAN	175.045			114.900		
	MIN, MAX	25.400, 730.384			4.562, 1263.455		
Week 3	5%, 95%	25.400, 730.384		NA	39.086, 1139.498		NA
	# of BLQ/ALQ Values	0/0			0/0		
	N	16			29		
	MEAN, GEO MEAN	220.431, 121.108			210.345, 108.820		
	SD, SE	211.2136, 52.8034			194.1911, 36.0604		
	MEDIAN	115.556			152.447		
Overall ^b	MIN, MAX	9.042, 626.981		NA	1.192, 674.143		NA
	5%, 95%	9.042, 626.981			2.466, 555.261		
	# of BLQ/ALQ Values	0/0			0/0		
	N	18			32		
	MEAN, GEO MEAN	209.357, 123.571			204.440, 130.280		
	SD, SE	199.7170, 47.0738			203.3880, 35.9543		
Overall ^c	MEDIAN	113.343		NA	126.735		NA
	MIN, MAX	7.501, 705.631			22.263, 756.966		
	5%, 95%	7.501, 705.631			29.150, 750.779		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438722

Final Draft: 22 October 2003

Page 753 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 63 of 264)

Biomarker: Nicotine-N-glucuronide (nmol/24hr) Analytical Lab: Harrogate

Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18	28	<.0001	31	34	<.0001
	MEAN, GEO MEAN	4026.806, 2152.393	5.227, NA		4140.122, 2380.428	1.243, NA	
	SD, SE	3521.3809, 829.9974	8.9670, 1.6946		4418.1241, 793.5185	4.2370, 0.7266	
	MEDIAN	3048.346	0.000		2576.293	0.000	
	MIN, MAX	25.209, 10788.304	0.000, 29.594		162.756, 22030.628	0.000, 22.042	
	5%, 95%	25.209, 10788.304	0.000, 29.242		185.043, 11202.823	0.000, 11.235	
	# of BLQ/ALQ Values	0/0	18/0		0/0	33/0	
Week 2	N	17	29	<.0001	31	34	<.0001
	MEAN, GEO MEAN	4025.196, 2885.683	12.807, NA		4619.799, 2660.685	0.838, NA	
	SD, SE	3025.1895, 733.7162	52.2807, 9.7083		4867.0677, 874.1512	3.7823, 0.6487	
	MEDIAN	3547.286	0.000		3511.091	0.000	
	MIN, MAX	461.543, 9872.580	0.000, 282.882		177.318, 22489.501	0.000, 21.701	
	5%, 95%	461.543, 9872.580	0.000, 23.674		193.519, 16921.539	0.000, 4.389	
	# of BLQ/ALQ Values	0/0	22/0		0/0	32/0	
Week 3	N	16	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	4351.611, 2285.075	4.535, NA		4485.523, 2581.348	0.432, NA	
	SD, SE	3671.9016, 917.9754	8.5750, 1.5656		3249.7743, 603.4679	1.5813, 0.2673	
	MEDIAN	3945.803	0.000		4005.325	0.000	
	MIN, MAX	28.428, 11461.291	0.000, 37.669		17.262, 12487.288	0.000, 8.114	
	5%, 95%	28.428, 11461.291	0.000, 21.208		52.296, 10420.453	0.000, 4.279	
	# of BLQ/ALQ Values	0/0	23/0		0/0	34/0	
Overall [*]	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	3965.133, 2293.944	7.466, NA		4289.753, 2765.078	0.839, NA	
	SD, SE	3288.3005, 775.0599	19.3413, 3.5312		3668.2894, 648.4681	2.6072, 0.4407	
	MEDIAN	3747.426	0.137		2982.790	0.000	
	MIN, MAX	26.819, 10353.310	0.000, 104.041		133.990, 15441.801	0.000, 11.885	
	5%, 95%	26.819, 10353.310	0.000, 21.634		199.791, 12852.562	0.000, 10.052	

^a P-value from Wilcoxon rank-sum test.^{*} Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438723

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 64 of 264)

Biomarker: Nicotine-N-glucuronide ((nmol/24hr)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18		NA	31		NA
	MEAN, GEO MEAN	270.600, 169.615			263.934, 185.085		
	SD, SE	245.2307, 57.8014			277.0427, 49.7583		
	MEDIAN	178.233			183.997		
	MIN, MAX	8.403, 837.161			12.336, 1295.919		
	5%, 95%	8.403, 837.161			65.416, 1120.282		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	17		NA	31		NA
	MEAN, GEO MEAN	288.580, 210.043			345.767, 216.978		
	SD, SE	235.5505, 57.1294			409.8456, 73.6104		
	MEDIAN	236.486			193.519		
	MIN, MAX	59.810, 832.306			19.617, 1880.171		
	5%, 95%	59.810, 832.306			59.106, 1188.730		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	16		NA	29		NA
	MEAN, GEO MEAN	330.168, 207.380			310.569, 186.744		
	SD, SE	258.1362, 64.5341			251.8602, 46.7693		
	MEDIAN	298.331			246.060		
	MIN, MAX	9.476, 851.592			3.452, 929.600		
	5%, 95%	9.476, 851.592			3.486, 741.273		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^c	N	18		NA	32		NA
	MEAN, GEO MEAN	282.614, 190.149			302.153, 221.251		
	SD, SE	217.4618, 51.2562			271.8673, 48.0598		
	MEDIAN	168.425			193.557		
	MIN, MAX	8.940, 724.671			43.896, 1230.708		
	5%, 95%	8.940, 724.671			69.230, 908.341		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^c Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438724

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 65 of 264)

Biomarker: Nicotine-N-glucuronide (nmol/mg Creatinine) Analytical Lab: Harrogate							
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	28	<.0001	31	34	<.0001
	MEAN, GEO MEAN	2.667, 1.629	0.003, NA		3.223, 2.054	0.001, NA	
	SD, SE	1.8782, 0.4427	0.0061, 0.0012		2.6290, 0.4722	0.0031, 0.0005	
	MEDIAN	2.644	0.000		3.131	0.000	
	MIN, MAX	0.024, 7.058	0.000, 0.023		0.135, 12.113	0.000, 0.016	
	5%, 95%	0.024, 7.058	0.000, 0.021		0.187, 7.068	0.000, 0.008	
	# of BLQ/ALQ Values	0/0	18/0		0/0	33/0	
Week 2	N	17	29	<.0001	31	34	<.0001
	MEAN, GEO MEAN	2.720, 2.069	0.011, NA		3.522, 2.113	0.001, NA	
	SD, SE	1.8726, 0.4542	0.0499, 0.0093		3.6051, 0.6475	0.0028, 0.0005	
	MEDIAN	2.323	0.000		2.864	0.000	
	MIN, MAX	0.298, 6.734	0.000, 0.270		0.153, 17.646	0.000, 0.016	
	5%, 95%	0.298, 6.734	0.000, 0.017		0.193, 11.734	0.000, 0.004	
	# of BLQ/ALQ Values	0/0	22/0		0/0	32/0	
Week 3	N	16	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	2.776, 1.558	0.002, NA		3.701, 2.200	0.001, NA	
	SD, SE	2.1773, 0.5443	0.0045, 0.0008		2.7698, 0.5143	0.0018, 0.0003	
	MEDIAN	2.549	0.000		3.179	0.000	
	MIN, MAX	0.025, 6.372	0.000, 0.021		0.020, 10.645	0.000, 0.008	
	5%, 95%	0.025, 6.372	0.000, 0.011		0.056, 9.700	0.000, 0.006	
	# of BLQ/ALQ Values	0/0	23/0		0/0	34/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	2.612, 1.659	0.006, NA		3.483, 2.345	0.001, NA	
	SD, SE	1.9175, 0.4520	0.0177, 0.0032		2.6610, 0.4704	0.0021, 0.0003	
	MEDIAN	2.521	0.000		2.952	0.000	
	MIN, MAX	0.025, 6.721	0.000, 0.097		0.120, 10.339	0.000, 0.009	
	5%, 95%	0.025, 6.721	0.000, 0.013		0.190, 9.409	0.000, 0.008	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438725

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 66 of 264)

Biomarker: Nicotine-N-glucuronide ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18		NA	31		NA
	MEAN, GEO MEAN	0.216, 0.128			0.205, 0.160		
	SD, SE	0.2139, 0.0504			0.1622, 0.0291		
	MEDIAN	0.137			0.144		
	MIN, MAX	0.008, 0.684			0.031, 0.713		
	5%, 95%	0.008, 0.684			0.062, 0.679		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	17		NA	31		NA
	MEAN, GEO MEAN	0.257, 0.151			0.259, 0.172		
	SD, SE	0.3877, 0.0940			0.2814, 0.0505		
	MEDIAN	0.123			0.165		
	MIN, MAX	0.043, 1.647			0.015, 1.304		
	5%, 95%	0.043, 1.647			0.051, 0.882		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	16		NA	29		NA
	MEAN, GEO MEAN	0.226, 0.141			0.265, 0.160		
	SD, SE	0.1834, 0.0458			0.2669, 0.0496		
	MEDIAN	0.155			0.191		
	MIN, MAX	0.008, 0.531			0.004, 1.213		
	5%, 95%	0.008, 0.531			0.004, 0.888		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	0.223, 0.138			0.245, 0.188		
	SD, SE	0.2319, 0.0547			0.2108, 0.0373		
	MEDIAN	0.127			0.194		
	MIN, MAX	0.008, 0.915			0.039, 1.065		
	5%, 95%	0.008, 0.915			0.091, 0.590		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438726

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 67 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (nmol/mg Creatinine)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	62.070, 44.228	0.095, NA		72.066, 53.384	0.053, 0.038	
	SD, SE	41.1904, 9.7087	0.1597, 0.0291		44.6144, 7.8868	0.0632, 0.0107	
	MEDIAN	54.596	0.033		66.924	0.033	
	MIN, MAX	0.762, 171.322	0.000, 0.677		1.870, 165.672	0.005, 0.340	
	5%, 95%	0.762, 171.322	0.016, 0.447		8.068, 162.785	0.017, 0.183	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	59.710, 41.943	0.178, NA		74.721, 57.970	0.056, 0.042	
	SD, SE	39.2615, 9.2540	0.5342, 0.0975		47.9812, 8.6177	0.0502, 0.0085	
	MEDIAN	50.999	0.038		64.581	0.033	
	MIN, MAX	0.520, 162.182	0.000, 2.938		5.674, 177.245	0.016, 0.243	
	5%, 95%	0.520, 162.182	0.011, 0.606		10.256, 175.663	0.017, 0.174	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	60.863, 40.299	0.064, 0.038		78.391, 62.940	0.051, 0.039	
	SD, SE	41.8253, 10.1441	0.0951, 0.0174		48.1753, 8.9459	0.0481, 0.0081	
	MEDIAN	51.737	0.030		63.710	0.033	
	MIN, MAX	0.402, 163.660	0.011, 0.470		10.306, 204.112	0.017, 0.283	
	5%, 95%	0.402, 163.660	0.016, 0.274		14.475, 177.849	0.017, 0.109	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	60.933, 43.007	0.113, 0.048		74.681, 58.662	0.053, 0.042	
	SD, SE	39.3367, 9.2717	0.2317, 0.0422		45.5234, 8.0475	0.0475, 0.0080	
	MEDIAN	58.041	0.034		66.336	0.039	
	MIN, MAX	0.561, 150.824	0.011, 1.222		5.950, 182.343	0.017, 0.236	
	5%, 95%	0.561, 150.824	0.013, 0.392		10.933, 163.962	0.017, 0.193	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438727

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 68 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites ((nmol/mg Creatinine)/cigarette per day)			Analytical Lab: Harrogate				
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	5.386, 3.485			4.725, 4.042		
	SD, SE	7.4367, 1.7528			2.9421, 0.5201		
	MEDIAN	3.417			3.973		
	MIN, MAX	0.254, 34.264			0.935, 14.783		
	5%, 95%	0.254, 34.264			1.986, 12.963		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	7.591, 3.322			5.495, 4.728		
	SD, SE	18.3926, 4.3352			3.2306, 0.5802		
	MEDIAN	3.239			4.715		
	MIN, MAX	0.173, 81.091			1.734, 15.686		
	5%, 95%	0.173, 81.091			2.051, 11.330		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	5.392, 3.790			5.287, 4.554		
	SD, SE	5.1386, 1.2463			3.6124, 0.6708		
	MEDIAN	4.092			4.413		
	MIN, MAX	0.134, 23.794			1.911, 20.287		
	5%, 95%	0.134, 23.794			2.024, 10.156		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	6.078, 3.610			5.238, 4.628		
	SD, SE	10.1725, 2.3977			2.9750, 0.5259		
	MEDIAN	3.583			4.388		
	MIN, MAX	0.187, 46.383			1.877, 16.312		
	5%, 95%	0.187, 46.383			2.556, 11.763		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438728

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 69 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (mg/24hr)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value*	Smokers	Non-Smokers	P-value*
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	13.822, 9.484	0.026, 0.011		13.303, 9.931	0.010, 0.007	
	SD, SE	9.9619, 2.3480	0.0420, 0.0077		8.3518, 1.4764	0.0092, 0.0016	
	MEDIAN	13.406	0.006		12.589	0.008	
	MIN, MAX	0.131, 43.641	0.003, 0.157		0.365, 34.676	0.002, 0.039	
	5%, 95%	0.131, 43.641	0.003, 0.148		2.343, 27.701	0.003, 0.038	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	13.093, 9.255	0.039, 0.013		15.102, 11.844	0.011, 0.008	
	SD, SE	7.5570, 1.7812	0.0940, 0.0172		8.8042, 1.5813	0.0087, 0.0015	
	MEDIAN	13.281	0.009		14.179	0.007	
	MIN, MAX	0.075, 33.112	0.002, 0.499		0.923, 36.320	0.002, 0.032	
	5%, 95%	0.075, 33.112	0.003, 0.190		2.125, 33.028	0.003, 0.029	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	14.745, 9.058	0.020, 0.011		14.494, 11.972	0.009, 0.007	
	SD, SE	11.6886, 2.8349	0.0289, 0.0053		7.2037, 1.3377	0.0066, 0.0011	
	MEDIAN	11.316	0.008		14.750	0.007	
	MIN, MAX	0.074, 41.355	0.004, 0.136		1.679, 29.438	0.003, 0.035	
	5%, 95%	0.074, 41.355	0.004, 0.078		2.178, 24.083	0.003, 0.026	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	13.929, 9.603	0.028, 0.013		13.936, 11.167	0.010, 0.008	
	SD, SE	9.1277, 2.1514	0.0474, 0.0087		7.6523, 1.3527	0.0069, 0.0012	
	MEDIAN	11.551	0.010		14.050	0.008	
	MIN, MAX	0.093, 37.247	0.003, 0.222		0.989, 27.579	0.003, 0.030	
	5%, 95%	0.093, 37.247	0.004, 0.135		2.359, 27.575	0.003, 0.026	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438729

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 70 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites ((mg/24hr)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	0.908, 0.748			0.892, 0.752		
	SD, SE	0.4563, 0.1076			0.6019, 0.1064		
	MEDIAN	0.800			0.777		
	MIN, MAX	0.044, 1.846			0.183, 3.468		
	5%, 95%	0.044, 1.846			0.273, 1.684		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	1.109, 0.733			1.124, 0.966		
	SD, SE	1.4161, 0.3338			0.7293, 0.1310		
	MEDIAN	0.832			0.893		
	MIN, MAX	0.025, 6.647			0.425, 3.670		
	5%, 95%	0.025, 6.647			0.437, 2.761		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	1.136, 0.853			0.957, 0.866		
	SD, SE	0.6417, 0.1556			0.4405, 0.0818		
	MEDIAN	1.085			0.881		
	MIN, MAX	0.025, 2.263			0.420, 2.007		
	5%, 95%	0.025, 2.263			0.429, 1.877		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	1.045, 0.802			0.988, 0.882		
	SD, SE	0.7335, 0.1729			0.5285, 0.0934		
	MEDIAN	0.890			0.955		
	MIN, MAX	0.031, 3.585			0.392, 3.005		
	5%, 95%	0.031, 3.585			0.424, 1.810		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438730

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2.2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 71 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (mg/mg Creatinine) Analytical Lab: Harrogate							
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	0.010, NA	0.000, NA		0.012, NA	0.000, NA	
	SD, SE	0.0068, 0.0016	0.0000, 0.0000		0.0073, 0.0013	0.0000, 0.0000	
	MEDIAN	0.009	0.000		0.011	0.000	
	MIN, MAX	0.000, 0.028	0.000, 0.000		0.000, 0.027	0.000, 0.000	
	5%, 95%	0.000, 0.028	0.000, 0.000		0.001, 0.026	0.000, 0.000	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	0.010, NA	0.000, NA		0.012, 0.009	0.000, NA	
	SD, SE	0.0063, 0.0015	0.0000, 0.0000		0.0078, 0.0014	0.0000, 0.0000	
	MEDIAN	0.009	0.000		0.010	0.000	
	MIN, MAX	0.000, 0.026	0.000, 0.000		0.001, 0.029	0.000, 0.000	
	5%, 95%	0.000, 0.026	0.000, 0.000		0.002, 0.028	0.000, 0.000	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	0.010, NA	0.000, NA		0.013, 0.010	0.000, NA	
	SD, SE	0.0068, 0.0017	0.0000, 0.0000		0.0078, 0.0014	0.0000, 0.0000	
	MEDIAN	0.008	0.000		0.010	0.000	
	MIN, MAX	0.000, 0.027	0.000, 0.000		0.002, 0.033	0.000, 0.000	
	5%, 95%	0.000, 0.027	0.000, 0.000		0.002, 0.029	0.000, 0.000	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	0.010, NA	0.000, NA		0.012, 0.010	0.000, NA	
	SD, SE	0.0064, 0.0015	0.0000, 0.0000		0.0074, 0.0013	0.0000, 0.0000	
	MEDIAN	0.009	0.000		0.011	0.000	
	MIN, MAX	0.000, 0.024	0.000, 0.000		0.001, 0.030	0.000, 0.000	
	5%, 95%	0.000, 0.024	0.000, 0.000		0.002, 0.027	0.000, 0.000	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 72 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites ((mg/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value*	Smokers	Non-Smokers	P-value*
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	0.001, NA			0.001, NA		
	SD, SE	0.0014, 0.0003			0.0006, 0.0001		
	MEDIAN	0.001			0.001		
	MIN, MAX	0.000, 0.006			0.000, 0.002		
	5%, 95%	0.000, 0.006			0.000, 0.002		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	0.001, NA			0.001, NA		
	SD, SE	0.0030, 0.0007			0.0007, 0.0001		
	MEDIAN	0.001			0.001		
	MIN, MAX	0.000, 0.013			0.000, 0.003		
	5%, 95%	0.000, 0.013			0.000, 0.002		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	0.001, NA			0.001, NA		
	SD, SE	0.0009, 0.0002			0.0007, 0.0001		
	MEDIAN	0.001			0.001		
	MIN, MAX	0.000, 0.004			0.000, 0.003		
	5%, 95%	0.000, 0.004			0.000, 0.002		
	# of BLQ/ALQ Values	0/0			0/0		
Overall*	N	18		NA	32		NA
	MEAN, GEO MEAN	0.001, NA			0.001, NA		
	SD, SE	0.0018, 0.0004			0.0007, 0.0001		
	MEDIAN	0.001			0.001		
	MIN, MAX	0.000, 0.008			0.000, 0.003		
	5%, 95%	0.000, 0.008			0.000, 0.002		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438732

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 73 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (nmol/24hr)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	85202.321, 58462.565	159.938, 67.755		82001.169, 61213.291	58.895, 44.579	
	SD, SE	61406.4097, 14473.6296	258.9385, 47.2755		51481.8797, 9100.7966	56.4888, 9.5484	
	MEDIAN	82633.120	37.278		77601.162	46.442	
	MIN, MAX	807.495, 269008.088	16.191, 965.245		2251.019, 213748.173	13.634, 237.553	
	5%, 95%	807.495, 269008.088	17.554, 910.691		14441.244, 170748.968	16.239, 234.212	
Week 2	# of BLQ/ALQ Values	0/0	0/0	<.0001	0/0	0/0	<.0001
	N	18	30		31	35	
	MEAN, GEO MEAN	80706.746, 57056.576	238.603, 79.085		93087.670, 73006.709	66.453, 50.878	
	SD, SE	46581.7789, 10979.4306	579.9512, 105.8841		54269.4223, 9747.0760	54.0386, 9.1342	
	MEDIAN	81866.447	55.334		87398.389	42.918	
	MIN, MAX	463.520, 204106.209	12.603, 3077.553		5691.880, 223877.537	14.343, 199.855	
Week 3	5%, 95%	463.520, 204106.209	15.682, 1170.521	<.0001	13096.445, 203586.824	19.348, 176.749	<.0001
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
	N	17	30		29	35	
	MEAN, GEO MEAN	90888.319, 55827.577	121.964, 68.946		89343.293, 73796.576	54.072, 44.842	
	SD, SE	72049.8950, 17474.6663	178.0699, 32.5110		44404.0636, 8245.6276	40.4937, 6.8447	
	MEDIAN	69754.394	48.161		90922.089	44.305	
Overall ^b	MIN, MAX	455.443, 254916.322	24.371, 838.565	<.0001	10347.744, 181459.213	17.387, 214.464	<.0001
	5%, 95%	455.443, 254916.322	25.818, 479.785		13427.500, 148449.107	18.202, 161.224	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
	N	18	30		32	35	
	MEAN, GEO MEAN	85861.395, 59208.644	173.501, 79.279		85905.064, 68833.445	59.807, 49.004	
	SD, SE	56264.4210, 13261.6512	292.4969, 53.4024		47169.5124, 8338.4705	42.7707, 7.2296	
Overall ^b	MEDIAN	71198.076	56.633	<.0001	86603.825	47.661	<.0001
	MIN, MAX	575.486, 229597.547	20.989, 1369.102		6096.881, 169098.026	16.995, 183.762	
	5%, 95%	575.486, 229597.547	21.248, 828.576		14539.033, 169972.601	20.862, 161.356	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438733

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 74 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites ((nmol/24hr)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	5597.160, 4607.020			5496.958, 4635.178		
	SD, SE	2813.1975, 663.0770			3710.2303, 655.8822		
	MEDIAN	4933.138			4786.547		
	MIN, MAX	269.165, 11381.236			1125.510, 21374.817		
	5%, 95%	269.165, 11381.236			1679.783, 10379.541		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	6832.907, 4519.371			6926.664, 5953.677		
	SD, SE	8729.3751, 2057.5334			4494.9220, 807.3118		
	MEDIAN	5129.101			5502.899		
	MIN, MAX	154.507, 40974.206			2619.289, 22620.758		
	5%, 95%	154.507, 40974.206			2696.009, 17016.199		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	7004.383, 5251.024			5899.075, 5338.755		
	SD, SE	3955.2792, 959.2961			2715.4895, 504.2537		
	MEDIAN	6687.793			5427.632		
	MIN, MAX	151.814, 13950.879			2586.936, 12370.759		
	5%, 95%	151.814, 13950.879			2642.015, 11572.851		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	6438.950, 4941.501			6088.668, 5435.886		
	SD, SE	4521.7761, 1065.7929			3257.9068, 575.9220		
	MEDIAN	5482.150			5888.948		
	MIN, MAX	191.829, 22102.107			2417.332, 18522.809		
	5%, 95%	191.829, 22102.107			2610.851, 11156.032		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438734

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 75 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (nmol/L)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	56466.8, 35719.0	92.9, 46.2		51422.5, 34962.7	31.8, 25.0	
	SD, SE	53151.00, 12527.81	158.41, 28.92		40492.71, 7158.17	31.63, 5.35	
	MEDIAN	39231.4	29.7		40087.7	17.6	
	MIN, MAX	572.7, 228943.1	17.1, 822.3		818.6, 185431.1	17.1, 165.0	
	5%, 95%	572.7, 228943.1	17.1, 346.0		5370.5, 117580.7	17.1, 116.9	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	60035.2, 40306.3	134.2, 50.9		64490.8, 44818.9	34.0, 27.3	
	SD, SE	49085.70, 11569.61	266.95, 48.74		54125.48, 9721.22	28.17, 4.76	
	MEDIAN	52177.3	31.1		48192.8	18.7	
	MIN, MAX	515.0, 226784.6	17.1, 1079.8		3118.8, 251547.8	17.1, 128.5	
	5%, 95%	515.0, 226784.6	17.1, 1035.9		10010.5, 175038.6	17.1, 112.3	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	49871.4, 33019.2	68.0, 39.3		55723.8, 43002.5	27.0, 23.0	
	SD, SE	34676.82, 8410.36	116.68, 21.30		37781.03, 7015.76	21.14, 3.57	
	MEDIAN	42119.1	28.9		47640.2	17.1	
	MIN, MAX	434.6, 124561.5	17.1, 645.0		5563.3, 161187.4	17.1, 123.5	
	5%, 95%	434.6, 124561.5	17.1, 165.5		9591.0, 129203.3	17.1, 60.8	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	56060.6, 39267.7	98.4, 50.7		55858.9, 41079.3	30.9, 26.1	
	SD, SE	38284.09, 9023.65	145.62, 26.59		40793.59, 7211.36	22.81, 3.86	
	MEDIAN	50201.9	38.5		43613.1	23.5	
	MIN, MAX	507.4, 175714.8	17.1, 555.8		3166.9, 177780.1	17.1, 110.3	
	5%, 95%	507.4, 175714.8	17.3, 482.6		8324.0, 129505.1	17.1, 100.4	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438735

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 76 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites ((nmol/L)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	3719.4, 2814.8			3348.5, 2647.4		
	SD, SE	2646.88, 623.88			2238.89, 395.78		
	MEDIAN	2775.4			2862.3		
	MIN, MAX	190.9, 10706.3			409.3, 8724.4		
	5%, 95%	190.9, 10706.3			879.4, 8428.7		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	5089.5, 3192.6			4614.6, 3655.0		
	SD, SE	5932.77, 1398.37			3421.37, 614.50		
	MEDIAN	3945.9			3777.3		
	MIN, MAX	171.7, 26435.0			1348.0, 13709.5		
	5%, 95%	171.7, 26435.0			1418.0, 13281.7		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	4966.7, 3105.8			3786.2, 3111.0		
	SD, SE	5840.25, 1416.47			2456.81, 456.22		
	MEDIAN	3429.6			2949.8		
	MIN, MAX	144.9, 24912.3			971.3, 11279.6		
	5%, 95%	144.9, 24912.3			1390.8, 7008.1		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	4572.0, 3243.8			3924.8, 3231.9		
	SD, SE	4155.78, 979.53			2526.51, 446.63		
	MEDIAN	3739.5			3502.5		
	MIN, MAX	169.2, 19091.7			1247.0, 11237.8		
	5%, 95%	169.2, 19091.7			1248.9, 9143.4		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438736

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 77 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites (mg/L) Analytical Lab: Harrogate							
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	9.2, 5.8	0.0, NA		8.4, 5.6	0.0, NA	
	SD, SE	8.61, 2.03	0.03, 0.00		6.57, 1.16	0.00, 0.00	
	MEDIAN	6.4	0.0		6.6	0.0	
	MIN, MAX	0.1, 37.1	0.0, 0.1		0.1, 30.1	0.0, 0.0	
	5%, 95%	0.1, 37.1	0.0, 0.1		0.9, 19.1	0.0, 0.0	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	9.8, 6.6	0.0, NA		10.5, 7.3	0.0, NA	
	SD, SE	7.96, 1.88	0.05, 0.01		8.78, 1.58	0.00, 0.00	
	MEDIAN	8.5	0.0		7.8	0.0	
	MIN, MAX	0.1, 36.8	0.0, 0.2		0.5, 40.8	0.0, 0.0	
	5%, 95%	0.1, 36.8	0.0, 0.2		1.6, 28.4	0.0, 0.0	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	8.1, 5.5	0.0, NA		9.0, 7.0	0.0, NA	
	SD, SE	5.63, 1.36	0.02, 0.00		6.12, 1.14	0.00, 0.00	
	MEDIAN	6.8	0.0		7.7	0.0	
	MIN, MAX	0.1, 20.2	0.0, 0.1		0.9, 26.1	0.0, 0.0	
	5%, 95%	0.1, 20.2	0.0, 0.0		1.6, 21.0	0.0, 0.0	
	# of BLQ/ALQ Values	0/0	0/0		0/0	0/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	9.1, 6.5	0.0, NA		9.1, 6.7	0.0, NA	
	SD, SE	6.21, 1.46	0.03, 0.01		6.62, 1.17	0.00, 0.00	
	MEDIAN	8.2	0.0		7.1	0.0	
	MIN, MAX	0.1, 28.5	0.0, 0.1		0.5, 28.8	0.0, 0.0	
	5%, 95%	0.1, 28.5	0.0, 0.1		1.4, 21.0	0.0, 0.0	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics).

PM3006438737

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 78 of 264)

Biomarker: Sum of Nicotine and Nicotine metabolites ((mg/L)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	0.6, NA			0.5, 0.4		
	SD, SE	0.43, 0.10			0.36, 0.06		
	MEDIAN	0.5			0.5		
	MIN, MAX	0.0, 1.7			0.1, 1.4		
	5%, 95%	0.0, 1.7			0.1, 1.4		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	0.8, NA			0.7, 0.6		
	SD, SE	0.97, 0.23			0.56, 0.10		
	MEDIAN	0.7			0.6		
	MIN, MAX	0.0, 4.3			0.2, 2.2		
	5%, 95%	0.0, 4.3			0.2, 2.2		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	0.8, NA			0.6, 0.5		
	SD, SE	0.94, 0.23			0.39, 0.07		
	MEDIAN	0.6			0.5		
	MIN, MAX	0.0, 4.0			0.2, 1.8		
	5%, 95%	0.0, 4.0			0.2, 1.1		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	0.7, NA			0.6, 0.5		
	SD, SE	0.67, 0.16			0.41, 0.07		
	MEDIAN	0.7			0.6		
	MIN, MAX	0.0, 3.1			0.2, 1.8		
	5%, 95%	0.0, 3.1			0.2, 1.5		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438738

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 79 of 264)

Biomarker: Total 3-hydroxycotinine (µg/24hr)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	8481.670, 5058.786	12.639, 5.259		7465.196, 5530.506	4.663, 3.147	
	SD, SE	7495.7959, 1766.7760	19.7909, 3.6133		5073.8646, 896.9410	5.5203, 0.9331	
	MEDIAN	7795.655	3.555		7094.738	2.800	
	MIN, MAX	80.370, 31233.615	0.950, 84.568		185.625, 21231.840	0.800, 25.920	
	5%, 95%	80.370, 31233.615	1.030, 59.985		1264.620, 17386.180	1.140, 19.728	
	# of BLQ/ALQ Values	0/0	8/0		0/0	15/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	7771.087, 5070.702	18.479, 6.526		9033.252, 6974.017	5.648, 3.680	
	SD, SE	5217.2058, 1229.7072	36.8337, 6.7249		5553.5372, 997.4447	6.3066, 1.0660	
	MEDIAN	7298.235	3.674		8284.165	2.795	
	MIN, MAX	48.420, 20994.570	1.000, 191.422		504.248, 22147.192	1.050, 24.208	
	5%, 95%	48.420, 20994.570	1.023, 74.670		1171.885, 19677.560	1.240, 23.013	
	# of BLQ/ALQ Values	0/0	2/0		0/0	13/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	8564.710, 4903.589	12.223, 5.533		8436.228, 6644.598	4.361, 3.162	
	SD, SE	7430.9813, 1802.2777	20.2196, 3.6916		5351.4056, 993.7311	4.4083, 0.7451	
	MEDIAN	6563.699	3.665		7278.863	2.870	
	MIN, MAX	52.295, 27454.900	1.430, 89.830		1258.180, 19074.831	1.068, 21.688	
	5%, 95%	52.295, 27454.900	1.720, 55.313		1308.324, 17880.045	1.089, 14.840	
	# of BLQ/ALQ Values	0/0	7/0		0/0	18/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	8308.200, 5267.651	14.447, 6.474		8107.255, 6415.476	4.891, 3.558	
	SD, SE	6258.3618, 1475.1100	22.2395, 4.0604		5035.7608, 890.2051	4.5939, 0.7765	
	MEDIAN	6721.081	5.076		7035.315	2.883	
	MIN, MAX	60.362, 23472.750	1.318, 97.065		666.066, 20817.954	1.067, 20.305	
	5%, 95%	60.362, 23472.750	1.374, 66.991		1386.126, 16456.732	1.303, 18.212	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438739

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 80 of 264)

Biomarker: Total 3-hydroxycotinine (nmol/24hr) Analytical Lab: Harrogate

Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	44130.128, 26320.861	65.762, 27.363		38841.414, 28775.223	24.263, 16.373	
	SD, SE	39000.6263, 9192.5358	102.9721, 18.8001		26399.3178, 4666.7842	28.7220, 4.8549	
	MEDIAN	40560.793	18.497		36913.920	14.568	
	MIN, MAX	418.165, 162508.499	4.943, 440.007		965.807, 110469.264	4.162, 134.862	
	5%, 95%	418.165, 162508.499	5.359, 312.102		6579.818, 90460.295	5.931, 102.645	
	# of BLQ/ALQ Values	0/0	8/0		0/0	15/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	40432.968, 26382.858	96.144, 33.953		47000.013, 36285.812	29.385, 19.145	
	SD, SE	27145.1218, 6398.1666	191.6461, 34.9896		28895.0539, 5189.7049	32.8133, 5.5465	
	MEDIAN	37972.717	19.113		43102.510	14.542	
	MIN, MAX	251.929, 109234.748	5.203, 995.969		2623.602, 115231.840	5.463, 125.954	
	5%, 95%	251.929, 109234.748	5.323, 388.508		6097.318, 102382.345	6.452, 119.737	
	# of BLQ/ALQ Values	0/0	2/0		0/0	13/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	44562.185, 25513.374	63.595, 28.790		43893.696, 34571.846	22.692, 16.452	
	SD, SE	38663.3961, 9377.2509	105.2024, 19.2072		27843.3632, 5170.3827	22.9362, 3.8769	
	MEDIAN	34150.926	19.069		37871.924	14.933	
	MIN, MAX	272.091, 142847.845	7.440, 467.385		6546.311, 99246.346	5.557, 112.843	
	5%, 95%	272.091, 142847.845	8.949, 287.794		6807.210, 93029.874	5.666, 77.213	
	# of BLQ/ALQ Values	0/0	7/0		0/0	18/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	43227.562, 27407.581	75.167, 33.685		42182.049, 33379.721	25.447, 18.511	
	SD, SE	32562.2568, 7674.9975	115.7120, 21.1260		26201.0638, 4631.7375	23.9026, 4.0403	
	MEDIAN	34969.785	26.410		36604.744	15.002	
	MIN, MAX	314.062, 122128.717	6.859, 505.029		3465.540, 108315.817	5.550, 105.649	
	5%, 95%	314.062, 122128.717	7.151, 348.552		7212.012, 85624.375	6.778, 94.757	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438740

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 81 of 264)

Biomarker: Total 3-hydroxycotinine ((µg/24hr)/cigarette per day)		Analytical Lab: Harrogate			
Timepoint	Statistic	Male		P-value ^a	
		Smokers	Non-Smokers		
Week 1	N	18		NA	32
	MEAN, GEO MEAN	518.293, 398.647			514.451, 418.780
	SD, SE	265.0141, 62.4644			361.5090, 63.9064
	MEDIAN	497.403			411.498
	MIN, MAX	26.790, 1041.121			92.813, 1738.618
	5%, 95%	26.790, 1041.121			148.548, 1220.408
	# of BLQ/ALQ Values	0/0			0/0
Week 2	N	18		NA	31
	MEAN, GEO MEAN	632.378, 401.643			674.091, 568.729
	SD, SE	761.0430, 179.3796			426.5924, 76.6183
	MEDIAN	500.314			535.339
	MIN, MAX	16.140, 3571.898			226.150, 1837.330
	5%, 95%	16.140, 3571.898			234.377, 1632.510
	# of BLQ/ALQ Values	0/0			0/0
Week 3	N	17		NA	29
	MEAN, GEO MEAN	686.349, 461.222			537.154, 480.698
	SD, SE	480.7707, 116.6040			277.6903, 51.5658
	MEDIAN	606.335			478.038
	MIN, MAX	17.432, 1676.349			222.522, 1418.901
	5%, 95%	17.432, 1676.349			224.937, 1089.147
	# of BLQ/ALQ Values	0/0			0/0
Overall ^b	N	18		NA	32
	MEAN, GEO MEAN	608.687, 437.008			577.776, 504.000
	SD, SE	432.0203, 101.8282			326.0893, 57.6450
	MEDIAN	539.388			481.105
	MIN, MAX	20.121, 2030.196			199.073, 1516.938
	5%, 95%	20.121, 2030.196			215.772, 1303.658

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438741

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 82 of 264)

Biomarker: Total 3-hydroxycotinine ((nmol/24hr)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	2696.680, 2074.160			2676.690, 2178.910		
	SD, SE	1378.8686, 325.0025			1880.9313, 332.5048		
	MEDIAN	2587.989			2141.025		
	MIN, MAX	139.388, 5416.950			482.904, 9046.030		
	5%, 95%	139.388, 5416.950			772.896, 6349.783		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	3290.262, 2089.748			3507.296, 2959.098		
	SD, SE	3959.7063, 933.3117			2219.5603, 398.6448		
	MEDIAN	2603.135			2785.367		
	MIN, MAX	83.976, 18584.583			1176.658, 9559.628		
	5%, 95%	83.976, 18584.583			1219.464, 8493.950		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	3571.073, 2399.735			2794.814, 2501.073		
	SD, SE	2501.4498, 606.6907			1444.8224, 268.2968		
	MEDIAN	3154.763			2487.232		
	MIN, MAX	90.697, 8722.043			1157.784, 7382.540		
	5%, 95%	90.697, 8722.043			1170.349, 5666.830		
	# of BLQ/ALQ Values	0/0			0/0		
Overall*	N	18		NA	32		NA
	MEAN, GEO MEAN	3166.997, 2273.752			3006.169, 2622.312		
	SD, SE	2247.8017, 529.8119			1696.6422, 299.9268		
	MEDIAN	2806.435			2503.186		
	MIN, MAX	104.687, 10563.111			1035.779, 7892.630		
	5%, 95%	104.687, 10563.111			1122.662, 6782.931		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438742

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 83 of 264)

Biomarker: Total 3-hydroxycotinine (ug/mg Creatinine)		Analytical Lab: Harrogate					
Timepoint	Statistic	Smokers	Non-Smokers	P-value*	Smokers	Non-Smokers	P-value*
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	5.847, 3.827	0.008, NA		6.788, 4.823	0.004, 0.003	
	SD, SE	4.1160, 0.9701	0.0122, 0.0022		4.9747, 0.8794	0.0069, 0.0012	
	MEDIAN	5.353	0.002		5.406	0.002	
	MIN, MAX	0.076, 15.997	0.000, 0.052		0.154, 18.383	0.001, 0.037	
	5%, 95%	0.076, 15.997	0.001, 0.042		0.676, 18.231	0.001, 0.022	
	# of BLQ/ALQ Values	0/0	8/0		0/0	15/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	5.688, 3.726	0.011, NA		7.402, 5.538	0.005, 0.003	
	SD, SE	4.0901, 0.9640	0.0217, 0.0040		5.3130, 0.9542	0.0060, 0.0010	
	MEDIAN	4.759	0.004		5.898	0.002	
	MIN, MAX	0.054, 15.619	0.000, 0.099		0.503, 20.024	0.001, 0.027	
	5%, 95%	0.054, 15.619	0.001, 0.071		0.918, 18.908	0.001, 0.021	
	# of BLQ/ALQ Values	0/0	2/0		0/0	13/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	5.880, 3.539	0.006, 0.003		7.537, 5.667	0.004, 0.003	
	SD, SE	4.7052, 1.1412	0.0104, 0.0019		5.6364, 1.0466	0.0050, 0.0008	
	MEDIAN	5.037	0.002		4.992	0.002	
	MIN, MAX	0.046, 17.626	0.001, 0.050		1.148, 23.294	0.001, 0.029	
	5%, 95%	0.046, 17.626	0.001, 0.026		1.303, 17.524	0.001, 0.010	
	# of BLQ/ALQ Values	0/0	7/0		0/0	18/0	
Overall†	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	5.814, 3.797	0.008, 0.004		7.186, 5.455	0.004, 0.003	
	SD, SE	4.1774, 0.9846	0.0125, 0.0023		5.1148, 0.9042	0.0053, 0.0009	
	MEDIAN	4.913	0.003		5.573	0.002	
	MIN, MAX	0.059, 16.414	0.001, 0.046		0.653, 20.195	0.001, 0.026	
	5%, 95%	0.059, 16.414	0.001, 0.039		0.914, 17.186	0.001, 0.021	

* P-value from Wilcoxon rank-sum test.

† Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438743

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 84 of 264)

Biomarker: Total 3-hydroxycotinine (nmol/mg Creatinine)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value*	Smokers	Non-Smokers	P-value*
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	30.420, 19.913	0.039, NA		35.319, 25.093	0.023, 0.014	
	SD, SE	21.4154, 5.0476	0.0638, 0.0116		25.8835, 4.5756	0.0358, 0.0061	
	MEDIAN	27.849	0.010		28.128	0.010	
	MIN, MAX	0.395, 83.232	0.000, 0.271		0.801, 95.647	0.005, 0.193	
	5%, 95%	0.395, 83.232	0.005, 0.219		3.517, 94.856	0.005, 0.114	
	# of BLQ/ALQ Values	0/0	8/0		0/0	15/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	29.593, 19.388	0.059, NA		38.511, 28.813	0.025, 0.015	
	SD, SE	21.2809, 5.0160	0.1128, 0.0206		27.6433, 4.9649	0.0314, 0.0053	
	MEDIAN	24.761	0.019		30.687	0.010	
	MIN, MAX	0.281, 81.266	0.000, 0.515		2.617, 104.185	0.005, 0.140	
	5%, 95%	0.281, 81.266	0.005, 0.369		4.776, 98.378	0.005, 0.109	
	# of BLQ/ALQ Values	0/0	2/0		0/0	13/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	30.593, 18.410	0.032, 0.015		39.214, 29.486	0.021, 0.014	
	SD, SE	24.4813, 5.9376	0.0541, 0.0099		29.3260, 5.4457	0.0262, 0.0044	
	MEDIAN	26.208	0.010		25.973	0.010	
	MIN, MAX	0.239, 91.708	0.005, 0.260		5.973, 121.199	0.005, 0.151	
	5%, 95%	0.239, 91.708	0.005, 0.135		6.780, 91.177	0.005, 0.052	
	# of BLQ/ALQ Values	0/0	7/0		0/0	18/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	30.249, 19.747	0.043, 0.020		37.388, 28.380	0.023, 0.016	
	SD, SE	21.7351, 5.1230	0.0652, 0.0119		26.6119, 4.7044	0.0275, 0.0046	
	MEDIAN	25.563	0.016		28.996	0.012	
	MIN, MAX	0.305, 85.402	0.003, 0.241		3.399, 105.075	0.005, 0.135	
	5%, 95%	0.305, 85.402	0.005, 0.203		4.755, 89.417	0.005, 0.111	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438744

Final Draft: 22 October 2003

Page 775 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 85 of 264)

Biomarker: Total 3-hydroxycotinine ((µg/mg Creatinine)/cigarette per day) Analytical Lab: Harrogate

Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	0.457, 0.302			0.457, 0.365		
	SD, SE	0.5352, 0.1261			0.3435, 0.0607		
	MEDIAN	0.373			0.377		
	MIN, MAX	0.021, 2.536			0.077, 1.823		
	5%, 95%	0.021, 2.536			0.161, 1.054		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	0.683, 0.295			0.545, 0.452		
	SD, SE	1.5982, 0.3767			0.3337, 0.0599		
	MEDIAN	0.342			0.479		
	MIN, MAX	0.018, 7.069			0.139, 1.274		
	5%, 95%	0.018, 7.069			0.171, 1.211		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	0.551, 0.333			0.488, 0.410		
	SD, SE	0.6392, 0.1550			0.3344, 0.0621		
	MEDIAN	0.420			0.326		
	MIN, MAX	0.015, 2.859			0.151, 1.709		
	5%, 95%	0.015, 2.859			0.186, 1.165		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	0.559, 0.317			0.505, 0.428		
	SD, SE	0.9084, 0.2141			0.3106, 0.0549		
	MEDIAN	0.392			0.435		
	MIN, MAX	0.019, 4.155			0.163, 1.389		
	5%, 95%	0.019, 4.155			0.187, 1.346		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438745

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 86 of 264)

Biomarker: Total 3-hydroxycotinine ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	2.376, 1.569			2.376, 1.900		
	SD, SE	2.7846, 0.6563			1.7873, 0.3160		
	MEDIAN	1.940			1.960		
	MIN, MAX	0.107, 13.195			0.401, 9.486		
	5%, 95%	0.107, 13.195			0.839, 5.486		
Week 2	# of BLQ/ALQ Values	0/0			0/0		
	N	18		NA	31		NA
	MEAN, GEO MEAN	3.552, 1.536			2.833, 2.350		
	SD, SE	8.3151, 1.9599			1.7359, 0.3118		
	MEDIAN	1.780			2.490		
	MIN, MAX	0.094, 36.780			0.725, 6.629		
Week 3	5%, 95%	0.094, 36.780			0.890, 6.299		
	# of BLQ/ALQ Values	0/0			0/0		
	N	17		NA	29		NA
	MEAN, GEO MEAN	2.865, 1.732			2.538, 2.133		
	SD, SE	3.3257, 0.8066			1.7400, 0.3231		
	MEDIAN	2.184			1.695		
Overall ^b	MIN, MAX	0.080, 14.876			0.786, 8.891		
	5%, 95%	0.080, 14.876			0.969, 6.061		
	# of BLQ/ALQ Values	0/0			0/0		
	N	18		NA	32		NA
	MEAN, GEO MEAN	2.907, 1.649			2.625, 2.227		
	SD, SE	4.7263, 1.1140			1.6155, 0.2856		
Overall ^c	MEDIAN	2.037			2.263		
	MIN, MAX	0.102, 21.617			0.850, 7.227		
	5%, 95%	0.102, 21.617			0.974, 7.002		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438746

Final Draft: 22 October 2003

Page 777 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 87 of 264)

Biomarker: Total 3-hydroxycotinine (ng/mL)		Analytical Lab: Harrogate					
Timepoint	Statistic	Smokers	Male Non-Smokers	P-value ^a	Smokers	Female Non-Smokers	P-value ^a
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	5422.5, 3090.8	8.4, 3.6		4520.5, 3158.8	2.7, 1.8	
	SD, SE	6007.04, 1415.87	17.48, 3.19		3406.88, 602.26	3.64, 0.62	
	MEDIAN	3942.6	3.2		3835.6	1.1	
	MIN, MAX	57.0, 26581.8	1.0, 96.1		67.5, 15165.6	1.0, 18.0	
	5%, 95%	57.0, 26581.8	1.0, 21.5		547.1, 12291.4	1.0, 14.4	
	# of BLQ/ALQ Values	0/0	8/0		0/0	15/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	5759.2, 3582.1	13.2, 4.2		6105.6, 4281.4	3.0, 2.0	
	SD, SE	5203.34, 1226.44	31.84, 5.81		4702.90, 844.67	3.77, 0.64	
	MEDIAN	4781.9	2.7		4802.7	1.3	
	MIN, MAX	53.8, 23327.3	1.0, 169.4		276.3, 16335.0	1.0, 17.5	
	5%, 95%	53.8, 23327.3	1.0, 57.6		968.5, 16284.7	1.0, 13.6	
	# of BLQ/ALQ Values	0/0	2/0		0/0	13/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	4831.2, 2900.2	6.8, 3.1		5180.2, 3871.9	2.2, 1.6	
	SD, SE	3990.41, 967.82	12.95, 2.36		4458.33, 827.89	2.40, 0.41	
	MEDIAN	4218.2	2.5		3922.3	1.0	
	MIN, MAX	49.9, 14967.4	1.0, 69.1		703.4, 23404.7	1.0, 12.5	
	5%, 95%	49.9, 14967.4	1.0, 21.9		898.7, 11352.7	1.0, 6.9	
	# of BLQ/ALQ Values	0/0	7/0		0/0	18/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	5401.5, 3535.5	9.5, 4.2		5159.8, 3843.3	2.7, 1.9	
	SD, SE	4129.77, 973.40	16.09, 2.94		3827.67, 676.64	2.76, 0.47	
	MEDIAN	5004.8	3.5		3829.5	1.3	
	MIN, MAX	53.6, 18644.1	1.0, 66.3		349.1, 18285.0	1.0, 12.3	
	5%, 95%	53.6, 18644.1	1.0, 61.9		835.5, 11100.3	1.0, 11.3	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438747

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 88 of 264)

Biomarker: Total 3-hydroxycotinine (nmol/L)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	28213.3, 16081.4	43.9, 18.6		23520.0, 16435.2	13.9, 9.2	
	SD, SE	31254.64, 7366.79	90.93, 16.60		17726.02, 3133.55	18.94, 3.20	
	MEDIAN	20513.4	16.7		19956.6	5.7	
	MIN, MAX	296.6, 138305.1	5.2, 500.0		351.2, 78906.6	5.2, 93.7	
	5%, 95%	296.6, 138305.1	5.2, 111.9		2846.6, 63952.2	5.2, 74.9	
	# of BLQ/ALQ Values	0/0	8/0		0/0	15/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	29965.1, 18637.5	68.6, 21.8		31767.7, 22275.9	15.9, 10.3	
	SD, SE	27072.96, 6381.16	165.69, 30.25		24469.20, 4394.80	19.64, 3.32	
	MEDIAN	24880.2	14.1		24988.4	6.8	
	MIN, MAX	279.9, 121371.9	5.2, 881.4		1437.6, 84991.0	5.2, 91.1	
	5%, 95%	279.9, 121371.9	5.2, 299.7		5039.1, 84729.3	5.2, 70.8	
	# of BLQ/ALQ Values	0/0	2/0		0/0	13/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	25136.6, 15089.8	35.6, 16.4		26952.4, 20145.6	11.6, 8.4	
	SD, SE	20762.11, 5035.55	67.36, 12.30		23196.68, 4307.52	12.50, 2.11	
	MEDIAN	21947.3	12.8		20407.7	5.2	
	MIN, MAX	259.6, 77875.4	5.2, 359.5		3659.8, 121774.7	5.2, 65.0	
	5%, 95%	259.6, 77875.4	5.2, 113.9		4675.9, 59068.1	5.2, 35.9	
	# of BLQ/ALQ Values	0/0	7/0		0/0	18/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	28104.0, 18394.8	49.4, 22.0		26846.2, 19996.4	13.8, 9.9	
	SD, SE	21487.20, 5064.58	83.69, 15.28		19915.37, 3520.37	14.36, 2.43	
	MEDIAN	26040.0	18.2		19924.9	6.8	
	MIN, MAX	278.7, 97005.2	5.2, 344.8		1816.2, 95136.9	5.2, 64.0	
	5%, 95%	278.7, 97005.2	5.4, 322.2		4347.1, 57754.9	5.2, 58.8	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438748

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 89 of 264)

Biomarker: Total 3-hydroxycotinine ((ng/mL)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	336.1, 243.6			308.3, 239.2		
	SD, SE	236.01, 55.63			222.79, 39.38		
	MEDIAN	306.9			240.2		
	MIN, MAX	19.0, 886.1			33.8, 824.6		
	5%, 95%	19.0, 886.1			67.7, 794.9		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	477.4, 283.7			449.6, 349.1		
	SD, SE	543.13, 128.02			366.34, 65.80		
	MEDIAN	367.5			361.8		
	MIN, MAX	17.9, 2304.5			113.1, 1898.5		
	5%, 95%	17.9, 2304.5			124.6, 1113.5		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	510.7, 272.8			339.8, 280.1		
	SD, SE	703.82, 170.70			238.87, 44.36		
	MEDIAN	319.2			239.8		
	MIN, MAX	16.6, 2993.5			94.8, 1017.6		
	5%, 95%	16.6, 2993.5			122.3, 950.2		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	439.2, 290.4			371.6, 300.9		
	SD, SE	421.42, 99.33			266.90, 47.18		
	MEDIAN	379.5			284.2		
	MIN, MAX	17.8, 1912.2			104.8, 1253.8		
	5%, 95%	17.8, 1912.2			118.2, 924.4		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438749

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 90 of 264)

Biomarker: Total 3-hydroxycotinine ((nmol/L)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	1748.6, 1267.3			1604.1, 1244.5		
	SD, SE	1227.94, 289.43			1159.16, 204.91		
	MEDIAN	1596.7			1249.7		
	MIN, MAX	98.9, 4610.2			175.6, 4290.4		
	5%, 95%	98.9, 4610.2			352.3, 4135.8		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	2484.1, 1476.3			2339.4, 1816.6		
	SD, SE	2825.84, 666.06			1906.12, 342.35		
	MEDIAN	1912.0			1882.5		
	MIN, MAX	93.3, 11990.1			588.3, 9878.0		
	5%, 95%	93.3, 11990.1			648.0, 5793.7		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	2657.0, 1419.3			1768.2, 1457.4		
	SD, SE	3661.97, 888.16			1242.87, 230.79		
	MEDIAN	1661.0			1247.7		
	MIN, MAX	86.5, 15575.1			493.0, 5294.6		
	5%, 95%	86.5, 15575.1			636.1, 4943.7		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	2285.1, 1511.3			1933.4, 1565.3		
	SD, SE	2192.66, 516.81			1388.68, 245.49		
	MEDIAN	1974.4			1478.7		
	MIN, MAX	92.9, 9949.3			545.2, 6523.5		
	5%, 95%	92.9, 9949.3			614.7, 4809.9		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234* will be used as 1.234*) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438750

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 91 of 264)

Biomarker: Total Cotinine (pg/24hr) Analytical Lab: Harrogate

Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	4697.127, 3151.036	7.373, 3.378		4980.328, 3583.251	3.560, 2.536	
	SD, SE	3405.8661, 802.7703	10.9875, 2.0060		3510.2690, 620.5337	4.1082, 0.6944	
	MEDIAN	4337.910	1.985		4470.819	2.565	
	MIN, MAX	44.556, 14394.338	0.950, 46.593		100.100, 17099.775	0.570, 20.150	
	5%, 95%	44.556, 14394.338	1.030, 31.240		720.720, 10349.625	0.800, 16.174	
	# of BLQ/ALQ Values	0/0	11/0		0/0	22/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	4529.454, 3076.865	9.251, 3.780		5307.500, 4056.020	3.933, 2.847	
	SD, SE	2787.8435, 657.1010	17.8779, 3.2640		3484.5950, 625.8517	3.5793, 0.6050	
	MEDIAN	4738.128	3.046		5108.532	2.480	
	MIN, MAX	25.650, 11710.980	0.625, 95.190		240.900, 16352.593	0.750, 13.755	
	5%, 95%	25.650, 11710.980	0.820, 27.225		735.694, 14208.645	0.915, 12.760	
	# of BLQ/ALQ Values	0/0	12/0		0/0	20/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	5082.502, 3029.686	6.551, 3.654		5097.602, 4137.160	3.155, 2.484	
	SD, SE	3857.0403, 935.4697	9.7076, 1.7724		2623.3481, 487.1435	2.9360, 0.4963	
	MEDIAN	3803.840	2.654		5222.565	2.395	
	MIN, MAX	21.379, 13322.126	1.350, 43.940		520.428, 10294.830	0.990, 15.268	
	5%, 95%	21.379, 13322.126	1.430, 33.930		756.280, 9606.210	1.034, 11.925	
	# of BLQ/ALQ Values	0/0	14/0		0/0	25/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	4774.447, 3201.346	7.725, 3.939		5005.216, 3905.527	3.549, 2.768	
	SD, SE	3149.1211, 742.2550	11.0103, 2.0102		2989.8478, 528.5354	2.9976, 0.5067	
	MEDIAN	4549.285	2.795		5168.867	2.632	
	MIN, MAX	30.528, 13142.481	1.133, 48.539		287.143, 12691.083	0.967, 11.705	
	5%, 95%	30.528, 13142.481	1.193, 30.177		834.401, 10962.570	1.167, 11.541	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234' for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics).

PM3006438751

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 92 of 264)

Biomarker: Total Cotinine (nmol/24hr)		Analytical Lab: Harrugate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	26656.198, 17882.131	41.839, 19.170		28263.359, 20334.948	20.202, 14.390	
	SD, SE	19328.2899, 4555.7216	62.3538, 11.3842		19920.7764, 3521.5290	23.3141, 3.9408	
	MEDIAN	24617.640	11.265		25371.898	14.556	
	MIN, MAX	252.855, 81687.868	5.391, 264.415		568.068, 97041.223	3.235, 114.351	
	5%, 95%	252.855, 81687.868	5.845, 177.287		4090.086, 58734.122	4.540, 91.787	
	# of BLQ/ALQ Values	0/0	11/0		0/0	22/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	25704.650, 17461.209	52.500, 21.453		30120.061, 23017.914	22.322, 16.155	
	SD, SE	15821.0119, 3729.0483	101.4570, 18.5234		19775.0765, 3551.7086	20.3127, 3.4335	
	MEDIAN	26888.877	17.286		28990.919	14.074	
	MIN, MAX	145.564, 66459.812	3.547, 540.203		1367.108, 92800.965	4.256, 78.060	
	5%, 95%	145.564, 66459.812	4.654, 154.502		4175.063, 80634.060	5.193, 72.413	
	# of BLQ/ALQ Values	0/0	12/0		0/0	20/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	28843.196, 17193.472	37.175, 20.737		28928.891, 23478.382	17.902, 14.098	
	SD, SE	21888.7039, 5308.7905	55.0906, 10.0581		14887.5004, 2764.5394	16.6615, 2.8163	
	MEDIAN	21586.792	15.062		29638.056	13.592	
	MIN, MAX	121.326, 75603.065	7.661, 249.360		2953.429, 58423.160	5.618, 86.646	
	5%, 95%	121.326, 75603.065	8.115, 192.553		4291.889, 54515.242	5.868, 67.674	
	# of BLQ/ALQ Values	0/0	14/0		0/0	25/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	27094.985, 18167.650	43.838, 22.354		28404.604, 22163.866	20.142, 15.706	
	SD, SE	17871.2622, 4212.2969	62.4834, 11.4079		16967.3859, 2999.4384	17.0113, 2.8754	
	MEDIAN	25817.193	15.859		29333.321	14.935	
	MIN, MAX	173.248, 74583.582	6.432, 275.461		1629.535, 72021.894	5.486, 66.424	
	5%, 95%	173.248, 74583.582	6.772, 171.255		4735.227, 62212.586	6.621, 65.497	

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234^a will be used as 1.234^a) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438752

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 93 of 264)

Biomarker: Total Cotinine ((µg/24hr)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	317.798, 248.311			336.076, 271.330		
	SD, SE	202.3497, 47.6943			284.6036, 50.3113		
	MEDIAN	257.105			290.369		
	MIN, MAX	14.852, 761.880			50.050, 1709.978		
	5%, 95%	14.852, 761.880			67.906, 608.801		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	363.151, 243.714			401.127, 330.767		
	SD, SE	406.4886, 95.8103			316.2812, 56.8058		
	MEDIAN	273.776			299.705		
	MIN, MAX	8.550, 1900.378			154.802, 1578.738		
	5%, 95%	8.550, 1900.378			168.956, 1113.879		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	395.614, 284.965			349.524, 299.300		
	SD, SE	238.6764, 57.8875			205.2411, 38.1123		
	MEDIAN	397.482			266.882		
	MIN, MAX	7.126, 918.949			104.652, 870.428		
	5%, 95%	7.126, 918.949			130.107, 845.604		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	356.143, 267.708			360.842, 307.890		
	SD, SE	237.1620, 55.8996			244.4457, 43.2123		
	MEDIAN	280.147			273.036		
	MIN, MAX	10.176, 1032.382			123.497, 1378.107		
	5%, 95%	10.176, 1032.382			140.352, 735.186		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438753

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 94 of 264)

Biomarker: Total Cotinine ((nmol/24hr)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	1803.502, 1409.164			1907.232, 1539.798		
	SD, SE	1148.3342, 270.6650			1615.1252, 285.5165		
	MEDIAN	1459.071			1647.840		
	MIN, MAX	84.285, 4323.669			284.034, 9704.122		
	5%, 95%	84.285, 4323.669			385.369, 3454.948		
Week 2	# of BLQ/ALQ Values	0/0			0/0		
	N	18		NA	31		NA
	MEAN, GEO MEAN	2060.879, 1383.077			2276.398, 1877.105		
	SD, SE	2306.8222, 543.7232			1794.8960, 322.3728		
	MEDIAN	1553.675			1700.826		
	MIN, MAX	48.521, 10784.643			878.503, 8959.340		
Week 3	5%, 95%	48.521, 10784.643			958.827, 6321.264		
	# of BLQ/ALQ Values	0/0			0/0		
	N	17		NA	29		NA
	MEAN, GEO MEAN	2245.111, 1617.182			1983.549, 1698.525		
	SD, SE	1354.4876, 328.5115			1164.7429, 216.2873		
	MEDIAN	2255.712			1514.553		
Overall ^b	MIN, MAX	40.442, 5215.035			593.900, 4939.676		
	5%, 95%	40.442, 5215.035			738.357, 4798.800		
	# of BLQ/ALQ Values	0/0			0/0		
	N	18		NA	32		NA
	MEAN, GEO MEAN	2021.113, 1519.244			2047.778, 1747.273		
	SD, SE	1345.8940, 317.2302			1387.2286, 245.2297		
Overall ^c	MEDIAN	1589.832			1549.477		
	MIN, MAX	57.749, 5858.764			700.849, 7820.754		
	5%, 95%	57.749, 5858.764			796.500, 4172.178		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438754

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 95 of 264)

Biomarker: Total Cotinine (µg/mg Creatinine)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	3.409, 2.384	0.005, NA		4.265, 3.125	0.003, NA	
	SD, SE	2.1337, 0.5029	0.0074, 0.0014		2.5826, 0.4565	0.0036, 0.0006	
	MEDIAN	3.233	0.001		4.284	0.002	
	MIN, MAX	0.042, 8.403	0.000, 0.033		0.083, 10.371	0.000, 0.015	
	5%, 95%	0.042, 8.403	0.001, 0.021		0.473, 8.958	0.001, 0.014	
	# of BLQ/ALQ Values	0/0	11/0		0/0	22/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	3.265, 2.263	0.007, NA		4.176, 3.220	0.003, 0.002	
	SD, SE	1.9738, 0.4652	0.0164, 0.0030		2.7789, 0.4991	0.0031, 0.0005	
	MEDIAN	2.968	0.002		3.723	0.002	
	MIN, MAX	0.029, 7.522	0.000, 0.091		0.240, 12.831	0.001, 0.015	
	5%, 95%	0.029, 7.522	0.001, 0.015		0.636, 9.853	0.001, 0.009	
	# of BLQ/ALQ Values	0/0	12/0		0/0	20/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	3.363, 2.188	0.004, 0.002		4.440, 3.529	0.003, 0.002	
	SD, SE	2.1802, 0.5288	0.0054, 0.0010		2.7980, 0.5196	0.0035, 0.0006	
	MEDIAN	2.961	0.002		3.807	0.002	
	MIN, MAX	0.019, 7.284	0.001, 0.025		0.518, 11.859	0.001, 0.020	
	5%, 95%	0.019, 7.284	0.001, 0.019		0.832, 10.517	0.001, 0.008	
	# of BLQ/ALQ Values	0/0	14/0		0/0	25/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	3.344, 2.331	0.005, 0.002		4.291, 3.340	0.003, 0.002	
	SD, SE	2.0124, 0.4743	0.0083, 0.0015		2.6178, 0.4628	0.0030, 0.0005	
	MEDIAN	3.191	0.002		3.974	0.002	
	MIN, MAX	0.030, 7.123	0.001, 0.042		0.280, 10.694	0.001, 0.015	
	5%, 95%	0.030, 7.123	0.001, 0.018		0.733, 8.923	0.001, 0.010	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438755

Final Draft: 22 October 2003

Page 786 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 96 of 264)

Biomarker: Total Cotinine (nmol/mg Creatinine)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value*	Female		P-value*
		Smokers	Non-Smokers		Smokers	Non-Smokers	
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	19.343, 13.527	0.026, NA		24.206, 17.733	0.018, NA	
	SD, SE	12.1086, 2.8540	0.0420, 0.0077		14.6561, 2.5908	0.0202, 0.0034	
	MEDIAN	18.345	0.006		24.309	0.011	
	MIN, MAX	0.238, 47.687	0.000, 0.187		0.471, 58.855	0.000, 0.085	
	5%, 95%	0.238, 47.687	0.006, 0.119		2.684, 50.837	0.006, 0.079	
	# of BLQ/ALQ Values	0/0	11/0		0/0	22/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	18.530, 12.843	0.038, NA		23.701, 18.276	0.019, 0.014	
	SD, SE	11.2015, 2.6402	0.0932, 0.0170		15.7703, 2.8324	0.0173, 0.0029	
	MEDIAN	16.841	0.009		21.128	0.011	
	MIN, MAX	0.165, 42.687	0.000, 0.516		1.362, 72.816	0.006, 0.085	
	5%, 95%	0.165, 42.687	0.006, 0.085		3.609, 55.916	0.006, 0.051	
	# of BLQ/ALQ Values	0/0	12/0		0/0	20/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	19.086, 12.417	0.021, 0.012		25.199, 20.024	0.017, 0.013	
	SD, SE	12.3729, 3.0009	0.0306, 0.0056		15.8784, 2.9485	0.0196, 0.0033	
	MEDIAN	16.804	0.011		21.605	0.011	
	MIN, MAX	0.108, 41.337	0.006, 0.142		2.940, 67.300	0.006, 0.114	
	5%, 95%	0.108, 41.337	0.006, 0.108		4.722, 59.684	0.006, 0.045	
	# of BLQ/ALQ Values	0/0	14/0		0/0	25/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	18.974, 13.230	0.028, 0.014		24.354, 18.957	0.018, 0.014	
	SD, SE	11.4205, 2.6918	0.0475, 0.0087		14.8558, 2.6262	0.0170, 0.0029	
	MEDIAN	18.107	0.010		22.550	0.011	
	MIN, MAX	0.170, 40.425	0.004, 0.240		1.591, 60.690	0.004, 0.085	
	5%, 95%	0.170, 40.425	0.004, 0.104		4.162, 50.636	0.006, 0.057	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438756

Final Draft: 22 October 2003

Page 787 of 15260

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 97 of 264)

Biomarker: Total Cotinine ((µg/ng Creatinine)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	0.301, 0.188			0.281, 0.237		
	SD, SE	0.3833, 0.0904			0.1893, 0.0335		
	MEDIAN	0.159			0.232		
	MIN, MAX	0.014, 1.681			0.042, 1.037		
	5%, 95%	0.014, 1.681			0.098, 0.690		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	0.384, 0.180			0.313, 0.263		
	SD, SE	0.8490, 0.2001			0.2209, 0.0397		
	MEDIAN	0.178			0.242		
	MIN, MAX	0.010, 3.761			0.113, 1.095		
	5%, 95%	0.010, 3.761			0.123, 0.716		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	0.294, 0.205			0.316, 0.255		
	SD, SE	0.2489, 0.0604			0.2777, 0.0516		
	MEDIAN	0.199			0.233		
	MIN, MAX	0.006, 1.089			0.080, 1.482		
	5%, 95%	0.006, 1.089			0.120, 0.831		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	0.324, 0.196			0.308, 0.263		
	SD, SE	0.4792, 0.1129			0.2129, 0.0376		
	MEDIAN	0.194			0.241		
	MIN, MAX	0.010, 2.177			0.104, 1.205		
	5%, 95%	0.010, 2.177			0.111, 0.584		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438757

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 98 of 264)

Biomarker: Total Cotinine ((nmol/mg Creatinine)/cigarette per day)		Analytical Lab: Harrogate					
Timepoint	Statistic	Male		P-value ^a	Female		P-value ^a
		Smokers	Non-Smokers		Smokers	Non Smokers	
Week 1	N	18		NA	32		NA
	MEAN, GEO MEAN	1.710, 1.066			1.597, 1.343		
	SD, SE	2.1745, 0.5125			1.0751, 0.1900		
	MEDIAN	0.903			1.311		
	MIN, MAX	0.079, 9.537			0.236, 5.886		
	5%, 95%	0.079, 9.537			0.555, 3.918		
	# of BLQ/ALQ Values	0/0			0/0		
Week 2	N	18		NA	31		NA
	MEAN, GEO MEAN	2.178, 1.017			1.775, 1.490		
	SD, SE	4.8185, 1.1357			1.2531, 0.2251		
	MEDIAN	1.011			1.374		
	MIN, MAX	0.055, 21.344			0.639, 6.213		
	5%, 95%	0.055, 21.344			0.700, 4.063		
	# of BLQ/ALQ Values	0/0			0/0		
Week 3	N	17		NA	29		NA
	MEAN, GEO MEAN	1.668, 1.168			1.791, 1.449		
	SD, SE	1.4125, 0.3426			1.5764, 0.2927		
	MEDIAN	1.129			1.321		
	MIN, MAX	0.036, 6.180			0.455, 8.413		
	5%, 95%	0.036, 6.180			0.680, 4.718		
	# of BLQ/ALQ Values	0/0			0/0		
Overall ^b	N	18		NA	32		NA
	MEAN, GEO MEAN	1.837, 1.113			1.747, 1.493		
	SD, SE	2.7193, 0.6409			1.2081, 0.2136		
	MEDIAN	1.101			1.368		
	MIN, MAX	0.057, 12.354			0.588, 6.837		
	5%, 95%	0.057, 12.354			0.628, 3.315		

NOTE: Values listed were normalized by taking the original biomarker and dividing it by the number of cigarettes found in question 4 of the weekly survey for the corresponding week.

^a P-value from Wilcoxon rank-sum test.

^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., '<1.234' will be used as '1.234') for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438758

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 99 of 264)

Biomarker: Total Cotinine (ng/mL) Analytical Lab: Harrogate		Male			Female		
Timepoint	Statistic	Smokers	Non-Smokers	P-value*	Smokers	Non-Smokers	P-value*
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	3253.1, 1925.2	4.5, 2.3		3150.1, 2046.6	1.8, 1.4	
	SD, SE	3277.32, 772.47	7.06, 1.29		2736.60, 483.77	1.77, 0.30	
	MEDIAN	1979.1	1.5		2234.6	1.0	
	MIN, MAX	31.6, 12250.5	1.0, 35.5		36.4, 12610.5	1.0, 7.1	
	5%, 95%	31.6, 12250.5	1.0, 16.7		348.7, 8279.7	1.0, 6.7	
	# of BLQ/ALQ Values	0/0	11/0		0/0	22/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	3373.5, 2173.6	5.2, 2.4		3802.3, 2490.0	1.9, 1.5	
	SD, SE	2964.30, 698.69	7.93, 1.45		3672.50, 659.60	1.52, 0.26	
	MEDIAN	2387.9	1.5		2731.6	1.0	
	MIN, MAX	28.5, 13012.2	1.0, 33.4		132.0, 18373.7	1.0, 5.8	
	5%, 95%	28.5, 13012.2	1.0, 23.2		503.9, 9222.8	1.0, 5.5	
	# of BLQ/ALQ Values	0/0	12/0		0/0	20/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	2794.4, 1791.9	3.6, 2.1		3210.5, 2410.8	1.6, 1.3	
	SD, SE	1879.15, 455.76	6.18, 1.13		2211.83, 410.73	1.52, 0.26	
	MEDIAN	2377.4	1.4		2429.1	1.0	
	MIN, MAX	20.4, 5701.3	1.0, 33.8		279.8, 7919.1	1.0, 8.8	
	5%, 95%	20.4, 5701.3	1.0, 11.7		540.2, 7304.4	1.0, 4.5	
	# of BLQ/ALQ Values	0/0	14/0		0/0	25/0	
Overall*	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	3167.0, 2117.4	4.4, 2.5		3306.6, 2322.6	1.8, 1.5	
	SD, SE	2358.10, 555.81	5.89, 1.07		2691.91, 475.87	1.40, 0.24	
	MEDIAN	3091.3	1.8		2198.6	1.1	
	MIN, MAX	26.8, 9891.3	1.0, 27.1		149.4, 12581.8	1.0, 6.9	
	5%, 95%	26.8, 9891.3	1.0, 17.1		464.3, 7394.7	1.0, 5.5	

* P-value from Wilcoxon rank-sum test.

* Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438759

RSR

Protocol No. PM-8450

Covance CRU Study No. 12226-8450

Table 14.2.2-2
Statistical Comparison Between Smokers and Non-Smokers by Gender of 24-Hour Urine Biomarkers of Exposure by Timepoint and Overall
(Page 100 of 264)

Biomarker: Total Cotinine (nmol/L) Analytical Lab: Harrogate

Timepoint	Statistic	Male			Female		
		Smokers	Non-Smokers	P-value ^a	Smokers	Non-Smokers	P-value ^a
Week 1	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	18461.1, 10925.4	25.3, 13.1		17876.9, 11614.6	10.4, 8.1	
	SD, SE	18598.78, 4383.78	40.09, 7.32		15530.19, 2745.38	10.06, 1.70	
	MEDIAN	11231.4	8.3		12681.1	5.7	
	MIN, MAX	179.3, 69521.6	5.7, 201.5		206.6, 71564.6	5.7, 40.3	
	5%, 95%	179.3, 69521.6	5.7, 94.8		1978.9, 46987.3	5.7, 38.0	
	# of BLQ/ALQ Values	0/0	11/0		0/0	22/0	
Week 2	N	18	30	<.0001	31	35	<.0001
	MEAN, GEO MEAN	19144.4, 12334.9	29.5, 13.8		21577.8, 14130.7	10.8, 8.7	
	SD, SE	16822.38, 3965.07	44.99, 8.21		20841.45, 3743.24	8.63, 1.46	
	MEDIAN	13551.4	8.5		15501.8	5.7	
	MIN, MAX	161.7, 73844.2	5.7, 189.5		749.1, 104270.7	5.7, 32.9	
	5%, 95%	161.7, 73844.2	5.7, 131.7		2859.6, 52339.4	5.7, 31.2	
	# of BLQ/ALQ Values	0/0	12/0		0/0	20/0	
Week 3	N	17	30	<.0001	29	35	<.0001
	MEAN, GEO MEAN	15858.2, 10169.2	20.6, 11.8		18219.8, 13681.3	8.9, 7.2	
	SD, SE	10664.18, 2586.44	35.06, 6.40		12552.13, 2330.87	8.63, 1.46	
	MEDIAN	13491.7	7.7		13785.1	5.7	
	MIN, MAX	115.8, 32354.9	5.7, 191.8		1587.9, 44940.9	5.7, 49.9	
	5%, 95%	115.8, 32354.9	5.7, 66.4		3065.6, 41452.5	5.7, 25.5	
	# of BLQ/ALQ Values	0/0	14/0		0/0	25/0	
Overall ^b	N	18	30	<.0001	32	35	<.0001
	MEAN, GEO MEAN	17972.4, 12017.3	25.1, 14.2		18765.0, 13180.7	10.0, 8.3	
	SD, SE	13382.22, 3154.22	33.38, 6.09		15276.63, 2700.55	7.89, 1.33	
	MEDIAN	17543.0	10.3		12476.8	6.3	
	MIN, MAX	152.3, 56133.3	5.7, 153.6		847.9, 71401.7	5.7, 39.0	
	5%, 95%	152.3, 56133.3	5.7, 97.2		2634.7, 41965.1	5.7, 31.0	

^a P-value from Wilcoxon rank-sum test.^b Overall values calculated by first averaging the results across visits within a subject, then calculating the descriptive statistics across subjects. Count of BLQ/ALQ values does not apply as the BLQ/ALQ values were converted to the limit of the quantification (e.g., <1.234 will be used as 1.234) for the averages across visits within a subject thus eliminating all BLQ/ALQ values for the overall statistics.

PM3006438760